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A LIFE COURSE APPROACH TO HYSTERECTOMY:

Working towards an improved understanding of the predictors and long-term health consequences of a common surgical procedure

Rachel Cooper

Thesis submitted for the Degree of Doctor of Philosophy of the University of London

Department of Epidemiology and Public Health
University College London

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Abstract

The epidemiology of hysterectomy is not fully understood. This has allowed a long-standing, emotive debate about the necessity of this common surgical procedure to continue without resolution. This thesis informs the debate by examining some of the main potential predictors and long-term health consequences of hysterectomy, using a life course approach.

The National Survey of Health and Development, a cohort of 5,362 British males and females followed-up since birth in March 1946 was used. Of 1,797 women with appropriate data, 403 had undergone hysterectomy by age 57 years. Using survival analyses the associations between lifetime socioeconomic position, body mass index (BMI), reproductive characteristics and subsequent hysterectomy rates were investigated. Linear and logistic regression models were used to examine the relationships between hysterectomy and subsequent BMI, musculoskeletal and psychological health and quality of life.

Education, age at menarche, parity, irregular/infrequent menstrual cycles and BMI in adulthood all predicted subsequent hysterectomy rates independently of each other. The association between hysterectomy and higher subsequent BMI could be explained by the greater exposure to risk factors for poor health of hysterectomised women. This difference in risk profiles only partially explained associations found between young age at hysterectomy and poor musculoskeletal and psychological health. The majority of hysterectomised women believed that their hysterectomy had a positive effect on their quality of life.

This work suggests that hysterectomy rates are determined by a complex of factors that operate via medical need as well as supply and demand. The UK's Chief Medical Officer's recent call to reduce hysterectomy rates to the same low levels across all areas of the country may not be achievable or beneficial. Although there is no clear evidence to suggest that hysterectomy directly influences subsequent health, hysterectomised women are a defined group who may require more support to maintain good health with age.

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Abbreviations

BMD – Bone mass density

BMI – Body mass index

BWHHS – British Women's Heart and Health Study

CI - Confidence interval

CMO – Chief Medical Officer

CVD – Cardiovascular disease

FE – Further education

FSH – Follicle stimulating hormone

HRT – Hormone replacement therapy

MRC – Medical Research Council

NHS – National Health Service

NSHD – National Survey of Health and Development

OC – Oral contraceptive

OPCS – Office of Population Censuses and Surveys

RII – Relative index of inequality

SD – Standard deviation

SEP – Socioeconomic position

SES – Socioeconomic status

UK – United Kingdom

US – United States of America

Chapter 1: Introduction

1.1 Introduction

Hysterectomy, removal of the uterus, is one of the most commonly performed surgical procedures on women in countries across the world. In the UK, it is estimated that 20% of women will have undergone hysterectomy by at least age 60 years.[1-3] Controversy about the necessity of the procedure[4-6] which has existed since it was introduced persists, fuelled by a lack of consistent and reliable evidence about its predictors and long-term consequences.

The overall aim of this thesis was to improve our understanding of the predictors and long-term health consequences of hysterectomy given the large gaps in knowledge which exist, demonstrated in the literature reviews presented in this and subsequent chapters. This has been achieved through the epidemiological analysis of data from the Medical Research Council National Survey of Health and Development (MRC NSHD), the oldest British birth cohort, on whom a wealth of data appropriate for the study of hysterectomy is available. A life course approach was utilised in planning and performing these analyses. It is hoped that this will allow our understanding of the predictors and long-term health consequences of hysterectomy to be advanced further than has been achieved using more traditional epidemiological approaches.

In this chapter an introduction to hysterectomy is provided with a focus on the history of the procedure, the main reasons it is performed and a summary of the arguments for and against hysterectomy. In addition an introduction to life course epidemiology and the benefits of using this approach to study hysterectomy are described. An introduction to the NSHD including details of the data collection which was performed as part of the work for this thesis is then provided in chapter 2. The remainder of the thesis is split into two main sections, the first examines some of the main potential predictors of hysterectomy and the second, some of the potential long-term health consequences of hysterectomy.

The first chapter of the first of these major sections, chapter 3, is an introduction to the study of the predictors of hysterectomy. The following three chapters each examine a different set of potential predictors of hysterectomy before, in the final chapter of this section, chapter 7, the inter-relationships between the different predictors identified are examined.

The first chapter of the latter major section of the thesis, chapter 8, is an introduction to the health consequences of hysterectomy. Each of the following three chapters examines a different potential health consequence of hysterectomy.

To conclude the thesis, chapter 12 summarises the main findings, identifies the overall strengths, limitations and implications of the work and suggests directions for future research.

1.2 History of hysterectomy

It is widely reported that the first vaginal hysterectomy was performed at least 1,800 years ago by the Greek, Soranus, in around 120AD.[7-12] Evidence exists thereafter to suggest that this procedure was performed by physicians at various times over the centuries most usually because of prolapse and the resultant infection of the uterus,[7;8;10] although evidence of the first fully planned procedures were not documented until the early nineteenth century.[12;13]

The first planned abdominal operation to excise an organ, an ovary, was performed by McDowell in 1809.[7;10;14;15] This led on to the first abdominal hysterectomies which occurred when operations to remove ovaries proved more complicated than planned. Heath and Clay are attributed with performing the first of these in Manchester, England in 1843.[7;8;10-13] However, the first abdominal hysterectomy in which the woman survived was not performed until ten years later with the first fully planned abdominal hysterectomy taking place in the same year.[9;10;12]

Throughout the nineteenth century, hysterectomy, whether performed through the abdomen or vagina, the two main routes of procedure, was associated with a high risk of mortality.

Estimates suggest that for vaginal hysterectomy, mortality rates were as high as 90% in the 1830s although they had dropped to 15% by 1886 and 10% by 1890.[7] Mortality rates for abdominal hysterectomy remained high until more recently with estimates of mortality of 70% in 1880.[10] Due to these risks, it is suggested[7] that the procedure was all but abandoned for a time during the mid-nineteenth century. However, with the introduction and increased use of anaesthetics and antisepsis and the refinement of surgical techniques towards the end of the nineteenth century, mortality declined to more 'acceptable' levels and hysterectomy increased in popularity.[7;11;12] This decline in mortality continued throughout the twentieth century and by the middle of the century was estimated to be 2.5% for vaginal and 3% for abdominal hysterectomies.[11] With further medical advancements in the latter half of the twentieth century including the introduction of antibiotics, intravenous therapy and blood transfusion as well as an increasing number of specialists trained in the procedure, mortality fell to very low levels.[7]

From its crude beginnings with potentially very serious costs to the women undergoing what was a painful and gruesome procedure, medical advancements over 150 years have meant that hysterectomy can now be performed easily and routinely.

1.3 Reasons for hysterectomy

Hysterectomy is currently used as a treatment for a wide range of gynaecological conditions. The majority of hysterectomies performed are elective i.e. not for emergency reasons.[16]

In one of four studies of British women,[1;2;16;17] Vessey and colleagues[1] found that fibroids were the most common reason for hysterectomy, accounting for 38.5% of all hysterectomies performed in an Oxford-based cohort. Menstrual problems with no underlying pathology accounted for 35.3%, prolapse for 6.5% and cancer for only 5.6% of hysterectomies. In another Oxford-based study, Coulter and colleagues[16] found that 34.3% of all hysterectomies performed in 1991/2 were for menstrual disorders, 15.6% for fibroids and 16.2% for prolapse. Only 4.3% of all hysterectomies were performed for emergency reasons such as cancer and post-partum complications. Maresh and colleagues[2] in a national study examining hysterectomies performed between 1994 and 1995 found that

46% of hysterectomies were performed for dysfunctional uterine bleeding. For 35% of hysterectomies fibroids were reported. In another Oxford-based study[17] of 1,170 consecutive hysterectomies performed in one hospital between 1997 and 1999, 45% of hysterectomies were performed for menstrual disorders, 21% for pelvic tumours including fibroids, 17% for prolapse and 15% for malignant and pre-malignant conditions. A similar distribution of reasons for hysterectomy has also been found in analyses of US national health statistics collected between 1988 and 1993.[11]

Most women who consult their doctor with gynaecological problems do so because of their symptoms not the underlying condition[11] for example, for heavy menstrual bleeding rather than because they are aware that they have fibroids which are causing the bleeding. Further, a doctor's diagnosis of the underlying gynaecological condition may not match pathology reports resulting from an examination of the extracted uterus. Variation in the method of assignment of reason for hysterectomy will thus lead to variation in the prevalence of different reasons for hysterectomy between studies.[17] Despite this variation, in all studies which have examined it, fibroids, menstrual disorders, prolapse, endometriosis and cancer have been found to be the most common reasons for hysterectomy.

Symptoms of fibroids, as described by Carlson and colleagues,[18] include excessive bleeding, pelvic pain and symptoms related to pressure on surrounding organs. The development of fibroids after menarche and their shrinkage after menopause suggest that it is an oestrogen dependent condition although the pathogenesis is not fully understood.[19;20] Like fibroids, endometriosis is also oestrogen dependent.[21] This condition is characterised by the growth of endometrial tissue in areas other than the endometrial cavity.[19] Symptoms include pelvic pain, dysmenorrhea, dyspareunia and irregular bleeding.[18;21] Of those women who consult doctors because of menstrual problems and are not then diagnosed with fibroids or endometriosis often no underlying cause is found. In these cases women are said to have dysfunctional uterine bleeding (included under this term are the conditions menorrhagia, polymenorrhagia, metrorrhagia, menometrorrhagia, hypomenorrhea and polymenorrhea).[19] Study of this set of problems is limited by the lack of an underlying pathology and the difficulty in measuring blood loss objectively.

The different aetiologies of different gynaecological conditions result in variations in reasons for hysterectomy by age. As discussed by a number of authors,[8;11;16;17] in younger women menstrual problems are the most common reason for hysterectomy, fibroids and endometriosis, given their oestrogen dependence, are often indicated in hysterectomies performed between ages 30 and 55 years, whereas prolapse and cancer tend to be the reason for hysterectomy in older women.

1.4 Guidelines on the 'appropriate' reasons for hysterectomy

There are many conditions, including those described briefly above, for which hysterectomy can be used as a treatment. The choice over whether hysterectomy is used rather than an alternative, of which there are a growing number, is often discretionary with the only exceptions being cancer, some obstetric complications and more serious cases of prolapse.

As a number of authors[4;8;16;19;22] discuss, defining absolute reasons and deciding on the appropriateness of hysterectomy is difficult for a number of reasons. These include: the fact that hysterectomy was introduced and became a popular treatment prior to the rise of evidence-based medicine which demands evidence of benefits outweighing any costs before the procedure is introduced; the wide number of different costs and benefits to be considered; the different viewpoints of patients and doctors; the changing availability and acceptability of alternatives; and the lack of evidence on how these compare with hysterectomy.

In the UK there are currently no official guidelines for doctors and surgeons to follow regarding the acceptable indications for hysterectomy. A remit for guidelines was issued by the Department of Health and the Welsh Assembly Government to the National Institute of Clinical Excellence in March 2003 with publication expected in November 2006[23] but this was amended and the guidelines will now focus only on the treatment of heavy menstrual bleeding with publication delayed until January 2007.[24]

1.5 Changes in the reasons for hysterectomy considered appropriate over time

As there have never been any official guidelines on appropriate indications for hysterectomy in the UK it is difficult to assess how the acceptability of different reasons has changed over time. To assess how doctor's beliefs on reasons for hysterectomy were informed and the changes in these over the twentieth century, several editions of a widely used gynaecology text book published and revised regularly since 1919, entitled 'Diseases of women by ten teachers'[25-32] until 1971 and now as 'Gynaecology by ten teachers'[33-37] were examined.

In the first edition of the book[25] and several editions thereafter the authors reflect on past negative opinions of surgery and present a positive view of surgical intervention for fibroids,

'.....since a non-malignant tumour of slow growth and not of immediate danger in being dealt with, there is sure to be considerable divergence of opinion; for there will always be a school which will advise their patients to bear those ills they have rather than fly to others that they know not of, in the shape of surgical operations and post-operative complications. Indeed, this latter view was the generally accepted doctrine twenty-five or thirty years ago, when operation was not mooted till the woman's condition was such as to make her life unbearable. At that time it was quite a reasonable position to take up, because the operation mortality was such that the risk was not worth running until all other means of alleviation had been exhausted. At the present time this risk is enormously diminished and therefore, logically, surgical interference ought to be recommended so much the earlier. Furthermore, with improved results and consequent greater frequency of operation as well as the lessened dread that comes of familiarity, there is growing disinclination among patients to submit to a life of restricted activity when a means of escape of little risk is open to them.'[25] (p.339)

By the late 1940s authors were suggesting some caution with a need to first consider women's needs,

'Generally the conservative operation is to be preferred during the childbearing period of life, not only because it leaves intact the capability of childbearing, but also because many of these younger women justly resent the losing of an organ so peculiarly associated with the idea of femininity.'[30] (p.271)

Despite these slight changes over time, hysterectomy has and remains in all editions of the book a suggested treatment for all major gynaecological conditions.

1.6 The arguments for and against hysterectomy

Since it first came into widespread use in the nineteenth century various individuals and groups have expressed views for and against hysterectomy. These arguments, presented across the course of the nineteenth and twentieth century, have received varying amounts of publicity.

1.6.1 Arguments for hysterectomy

As will be described in chapter 3, rates of hysterectomy have increased over the twentieth century. In addition hysterectomy continues to be performed in large numbers. This suggests that there have been many proponents of the procedure.

In the 1960s Wright[38] held the extreme view that,

> 'The uterus has but one function: reproduction. After the last planned pregnancy, the uterus becomes a useless, bleeding, symptom-producing, potentially cancer-bearing organ and therefore should be removed.'[38] (p. 562)

While many other doctors were more conservative in their use of hysterectomy, there has been a general medical consensus that the benefits of hysterectomy, especially in more recent times with low levels of associated post-operative mortality and morbidity, outweigh the costs. The procedure is seen to be useful because it is very successful in relieving gynaecological symptoms.[21] Given gynaecological conditions are one of the ten most common reasons for consulting a general practitioner[39] it is perhaps not surprising that many doctors recommend hysterectomy. Unlike many alternatives where repeated treatments may be necessary due to the subsequent recurrence of gynaecological problems after treatment, hysterectomy is unlikely to result in women requiring further treatment. As Schaffer and Word[40] highlight, because hysterectomy is so effective in treating gynaecological complaints it will remain commonly used until similarly effective but less radical treatments are developed.

1.6.2 Arguments against hysterectomy

In the late nineteenth century some doctors voiced concern about the use of hysterectomy partly because of the associated high mortality at that time. Benrubi[7] quotes the German surgeon Dieffenback who wrote,

'To take the entire womb from the belly of a woman means the removal of that woman's soul. Still, some daring men attempted it and they deserve our thanks in as much as the results of their terrible operation furnish us all the proof needed to banish this procedure from the field of surgery. According to my opinion, an indication for this operation does not exist. The attempted expiration of the womb partakes more of the character of murder tales than of curative surgical operations.'[7] (p. 536)

Priestley[41] in an article in the British Medical Journal in 1895 suggested caution in using hysterectomy, providing examples of other procedures such as clitoridectomy which had been fashionable for a time but were later found to be of little benefit. He was greatly concerned that often doctors had too much zeal for performing surgery at the expense of considering other medical treatments and that there was a detrimental effect of this,

'Over-zeal in gynaecology is not so innocuous as the change in fashions of medicines....Operations may end life, or leave the patient crippled so far as some of the highest functions of life are concerned, and if they do not physically injure, they may at least leave her demoralised and mentally worse.'[41] (p. 286)

Despite such medical concerns and perhaps due to the improvements in the safety of the procedure over time, hysterectomy continued to increase in popularity. The need for caution was however, still acknowledged with Miller[42] in a lecture in 1945 suggesting the need to reassess the indications for which the procedure was performed,

'Once a rare and spectacular procedure performed by only a few skilled and courageous surgeons, the operation today has become quite commonplace. Similarly, the indications, once highly restricted, have been so broadened as to warrant scrutiny and re-evaluation. No one can deny the importance of hysterectomy....but one may question some of the present-day indications for its widespread performance. If enthusiasm for the operation has warped our judgment, it is not the first time this has happened.'[42] (p. 805)

Criticism of hysterectomy by most doctors has abated since the procedure's safety began to improve, however, the increasing use of hysterectomy caused feminist groups and others in the early part of the twentieth century to become concerned about the use of the procedure. As women were thought by many, in the nineteenth and early twentieth century, to be defined by their reproductive organs it was widely held that by removing these, doctors were depriving women of their natural role in society which had implications for individuals and for society as a whole.[43] It was also thought, given the important influence the uterus was believed to have over a woman, that hysterectomy was being used by misogynistic doctors who felt threatened by women to maintain control over them.[44;45] It has also been suggested that doctors medicalised many non-medical conditions such as menstruation in a bid to find more patients and illnesses to treat thereby guaranteeing their continued employment.[44] This latter argument has persisted and many people still believe that the treatments doctors choose to perform are influenced by their personal interests rather than those of the patient and, that male doctors use their power over women to use the treatments they prefer.[46]

Although the level of patient autonomy has increased in recent years and there are a greater number of female doctors, the legacy of earlier beliefs about the controlling influence of male doctors over female patients persist and feminist arguments against hysterectomy are still being proposed. The views of anti-hysterectomy groups are expressed and widely promoted in the media,[5;6;47-49] on the internet[50] and in books, with titles such as 'The ultimate rape'[51] and 'No more hysterectomies.'[52] Anti-hysterectomy groups include one in the UK known as the 'Campaign against hysterectomy.' In a book[53] by the head of this group, Simkin, a very one-sided argument against the use of hysterectomy is provided. While many arguments against hysterectomy are proposed, the potential benefits of hysterectomy for women with benign gynaecological conditions are overlooked perhaps because these are thought to be outweighed by the loss of a woman's gender identity, with Simkin stating that,

'Menstruation, however inconvenient, however painful and however heavy the bleeding is a monthly reminder of a woman's sexuality, femininity, youth and her ability to procreate, which she does not want to lose. This is central to a woman's psyche and dominates her physical, emotional and psychological functioning.'[53] (p. 25)

However, this view is not fully supported by empirical evidence, with research by Elson[54] finding that the majority of hysterectomised women she interviewed expressed relief rather than regret at the loss of their uterus and menstruation leading her to conclude that,

'hysterectomy does not have universal effects on the complex phenomenon of women's gender identity.'[54] (p.47)

This is supported by the findings from other studies which have also found that women do not regard the uterus as essential to their femininity[55] and do not frequently report the loss of the feeling of femininity after hysterectomy.[55-57]

This demonstrates the fact that many arguments against hysterectomy although potentially justified are based on flawed theories which may not be fully supported by empirical evidence when appropriately tested. Another example of the use of biased information and the highly emotive nature of this debate is found in the information provided by the American organisation Hysterectomy Educational Resources and Services foundation[50] which amongst a biased sample of self-selected hysterectomised women has found a high prevalence of a wide range of adverse effects of hysterectomy which it uses to argue against performing hysterectomy, referring to the procedure as 'surgical abuse.'

1.7 Summary

There is a clear need to consider how necessary hysterectomy is, especially given the elective nature of the procedure and, as will be discussed in chapter 3, that changes in hysterectomy rates over time and between places are unlikely to be fully explained by differences in the levels of gynaecological morbidity and therefore medical need for hysterectomy. However, many of the current arguments are based on no, very little or specifically selected scientific evidence. Discussions about how necessary hysterectomy is need to be informed by empirical evidence about the epidemiology of hysterectomy with full consideration given to the predictors and all costs and benefits of the procedure which have been assessed using appropriate scientific methodology. Until there is an improved evidence-base, groups arguing for and against hysterectomy can continue to promote their polarised views about hysterectomy without any hope of the debate being resolved. The people that suffer as a result of a failure to resolve this debate are the women facing important medical decisions who receive conflicting advice from different organisations and the medical profession.

This thesis aims to inform the debate by providing empirical evidence about some of the main predictors and long-term health consequences of hysterectomy in a British birth cohort, with additional justification for the study of these provided in subsequent chapters.

1.8 Life course epidemiology

The epidemiological study of hysterectomy may be informed by the use of a life course approach. Life course epidemiology has been defined by Kuh and Ben-Shlomo as,

> '...the study of long-term biological, behavioural and psychosocial processes that link adult health and disease risk to physical or social exposures acting during gestation, childhood, adolescence, earlier in adult life, or across generations.'[58] (p.3)

While researchers in other academic disciplines have utilised this approach for many years[59;60] and it is not a completely novel approach to the study of epidemiology, it is only within the last several years that the term 'life course epidemiology' has been coined and the approach has come to be widely used.[58]

Epidemiologists and public health specialists had, in the first half of the twentieth century, considered the importance of early life factors on adult health and mortality risk.[61] However, with the rise in incidence of chronic non-communicable diseases such as cardiovascular disease and lung cancer and, the continued poor health of adult populations despite the introduction of reforms which had reduced infant mortality rates and improved child health, the focus of epidemiological research switched to adult risk factors.

From World War II until the 1970s, epidemiological research was almost exclusively concerned with the investigation of adult risk factors, many of which could be classified as lifestyle factors, with little or no consideration given to factors in earlier life or across the life course.[61] While the adult lifestyle approach continued to prevail throughout the 1970s and 1980s, some researchers came to acknowledge that the establishment of adult lifestyle factors begins in childhood.[58] Others recognising the limitations of using an adult lifestyle risk factor model in trying to explain all variations in disease risk between different socioeconomic groups and places, looked to the possibility that there was a direct influence of early life factors on adult disease risk.

Forsdahl and Barker are two of the people often attributed with triggering the increase in interest in the importance of early life factors and are seen by many as providing the catalyst for the development of life course epidemiology.[60] Forsdahl, in the 1970s, proposed and found evidence of an association between adverse socioeconomic conditions in childhood and mortality risk in adulthood[62;63] which supported the idea of a need to consider early life factors. Barker and colleagues in Southampton, through their work using historical cohort studies developed and first tested the fetal origins hypothesis which states that,

'...fetal undernutrition in middle to late gestation, which leads to disproportionate fetal growth, programmes later coronary heart disease.'[64] (p.171)

This hypothesis was extended to include other chronic diseases and evidence of an inverse association between various markers of pre-natal and infant growth and cardiovascular and respiratory diseases, diabetes and their associated risk factors was found.[58] At first Barker's hypotheses were presented as a direct challenge to adult lifestyle models[61] and so, as described by Kuh and colleagues,[60] life course epidemiology was developed, with recognition of the importance of both to,

'counteract the increasing polarisation of biological programming in utero and adult lifestyle approaches to chronic disease aetiology.'[60] (p.778)

Epidemiologists rely for their work using a life course approach on the availability of data on individuals from across life, whether collected prospectively or retrospectively. Many of the historical cohort studies with such data have focused only on men, some because they are occupational cohorts, formed at times when many women did not work outside the home, others because of the original focus of many studies on cardiovascular disease which was initially thought to be a problem of middle-aged white men.[59] This is changing and with time more studies which include women are being conducted. As well as using a life course approach to examine pathways to health outcomes common to both sexes and also to study sex differences in common health outcomes, the approach is also being applied to the study of health outcomes specific to women such as breast cancer,[65;66] menopause[67;68] and gynaecological morbidity.[69]

The application of a life course approach to the study of women's health allows the integration of social and biological approaches which have previously been unhelpfully dichotomised and presented in competition with each other within this field of research.[59] This dichotomy arose when feminists in the 1960s developed social models to challenge the medical and biological models of women and their health developed since the nineteenth century by scientists and medical doctors. While recent work on women's health[70] has suggested the need to consider both social and biological approaches in order to advance our understanding of various outcomes, there has been little focus, until recently,[71] on studying both sets of factors across life. This is despite the potential benefits. By taking a much wider, interdisciplinary view of health outcomes and considering how the many different factors across life which are likely to contribute to health outcome risk act both together and independently it may be possible to move closer to elucidating the aetiology of various health outcomes and explain more fully variations in disease risk between different groups over time and place than has been achieved to date.

As will be detailed in chapter 3, hysterectomy is a health outcome potentially influenced by factors acting along both social and biological pathways all of which could be operating from early life onwards and across generations. Further, as will be discussed in chapter 8, the health outcomes often proposed as consequences of hysterectomy are also influenced by factors acting across life. A life course approach, will enable the role of the different biological and social pathways across life which may influence risk of hysterectomy and those subsequent health outcomes potentially associated with hysterectomy to be examined in more depth than could be achieved using more traditional approaches. The ultimate aim of this would be to improve women's health and wellbeing by informing policy and changes in medical practice.

Chapter 2: Introduction to the data

2.1 Introduction

To address the objectives defined in the following chapters, the main data source used is the MRC NSHD, alternatively known as the 1946 British birth cohort. This chapter describes the dataset focusing on details specific to this thesis. This is done before the main objectives are defined in subsequent chapters given choices about the analyses performed and the associations examined were determined to an extent by the data available.

The NSHD is the oldest of the four national birth cohort studies in the UK. A detailed account of the study and its findings to date have been published in an array of papers and books[72-78] and for brevity details of the study are only summarised below.

2.2 Background information

2.2.1 History of the study

At inception, the immediate aims of the NSHD, established by Dr J.W.B. Douglas, were to examine maternity services and the cost to families of having a baby to inform plans being made for the creation of the National Health Service (NHS) and, due to national concerns about declining fertility rates. Ironically the cohort members were born at the start of an unforeseen baby boom.[76] Members of this cohort have lived through a time of great social change being born immediately after World War II and immediately prior to the introduction, in 1948, of the NHS.[72]

2.2.2 Sampling frame

The NSHD consists of a representative sample of all births which occurred in England, Scotland and Wales between March 3rd and 9th 1946. Of the 16,695 births which occurred during this time 1,279 were in 34 (7.4%) local authorities which did not agree to participate in the survey. Of the remaining births, information was collected from 13,687 mothers. Due to concerns about the low number of multiple births (n=180) for use in statistical analyses and the difficulties of following-up illegitimate births (n=672) these were excluded. A stratified random sample of the remaining single, legitimate births was then made as not all the remaining children could be followed-up regularly given the available resources without compromising data quality. This was achieved by sampling all births to wives of non-manual and agricultural workers and a random one in four of the births to wives of manual workers creating a final sample size of 5,362 (2,547 females, 2,815 males), see figure 2.1.

2.2.3 Timing and methods of data collection

A wide range of data, including medical, psychological and socioeconomic information,[73] has been prospectively collected since the cohort members' births at time points across life and continues with new data collections planned. Figure 2.2 summarises the timing and methods employed at each of the data collection points and shows that most data have been collected during home visits or using postal questionnaires. As well as surveying all members of the cohort at regular time intervals across adulthood, the female members of the cohort have been surveyed under a project titled 'Women's Health in the Middle Years', using postal questionnaires sent annually between the ages of 47 and 54 years inclusive and at age 57 years.[77]

2.2.4 Follow-up and representativeness of the cohort

To ensure that the cohort remains as representative as possible it has been necessary to maintain high levels of follow-up, especially as loss to follow-up is often not random and can lead to the creation of smaller, more highly selected groups, introducing bias and limiting generalisability of findings. High levels of follow-up have been achieved in the NSHD despite the length of time over which the cohort have been followed due to the persistence with which study members have been traced, through the careful attempts made to keep cohort members interested in the study and by collecting much of the data during home visits.[72;74] As a result, the cohort remained fairly nationally representative when their circumstances at age 43[74] and 53 years,[76] were compared to equivalent census information, allowing for the fact that sample selection occurred prior to the high levels of immigration since witnessed in the UK and excluded all multiple and illegitimate births.

2.2.5 Benefits of the NSHD

The NSHD has many advantages over other studies especially for undertaking analyses using a life course approach. These include, the general benefits:

- data collection began at birth
- most data has been collected prospectively
- data has been collected relatively regularly and so there are no major time periods across life when data has not been collected prospectively
- much of the data has been collected by trained specialists
- a wide range of medical, social and psychological information has been collected
- some measures have been collected at a number of different time points across life and so changes in characteristics over time can be studied
- the sample was drawn from across the whole of England, Scotland and Wales rather than from a specific geographical area within the country
- the sample is population-based rather than selected from a clinic or hospital
- high levels of follow-up have been maintained

and, the benefits specific to this thesis:

- high quality data on many women's health outcomes and symptoms were collected annually during the period when women were at highest risk of undergoing hysterectomy
- all women have been exposed to the same social changes at the same ages
- the temporal nature of associations can be examined as measures of many characteristics are available both pre- and post-hysterectomy
- the cohort have reached an age by which most hysterectomies have now occurred

The only other studies in the UK with most of the same benefits as the NSHD are the other two national birth cohort studies to have reached adulthood but as these are younger many of the outcomes to be studied in this thesis have not occurred in sufficient number yet. Other studies in the UK which have collected data to be used for life course analyses while sharing some of the same benefits as the NSHD have far fewer benefits overall as they tend to rely heavily on retrospectively self-recalled measures or have long periods across life during which data collection has not taken place prospectively, have high loss to follow-up or are not nationally representative.

2.3 Information specific to this thesis

2.3.1 Study sample for analyses in the thesis

Given the focus of this thesis on hysterectomy, a procedure unique to women, only the female members of the cohort were eligible for inclusion in the dataset. Of the female members only those for whom information on hysterectomy status was available could be included in analyses. Information on hysterectomy status was requested at a number of data collection points between 1989 and 2003, inclusive, and so, to be eligible for inclusion women needed to have responded at least once during this time. Some women were not eligible to participate between these times because they had previously died, emigrated, permanently refused to participate or been lost, other women who were eligible failed to respond and others responded but failed to provide complete information about their hysterectomy status.

Figure 2.3 and table 2.1 show losses to follow-up of females in the cohort and demonstrate how the maximum available sample for the main analyses in this thesis, which is 1,797 women, was achieved.

2.3.2 Main variables used in analyses

2.3.2.1 Ascertainment of hysterectomy status

The main variable of interest in this thesis was hysterectomy status, in chapters 3 to 7 it was the main outcome and in chapters 8 to 11 the main explanatory variable.

Women were asked to respond to questions about their hysterectomy and oophorectomy status between the ages of 43 and 57 years (1989 and 2003) at each data collection during this time period. (Oophorectomy is surgical removal of the ovaries and is regularly performed at the same time as hysterectomy, often as a prophylaxis for ovarian cancer.[79] Removal of both ovaries is called a bilateral oophorectomy and removal of only one ovary is known as a unilateral oophorectomy).

During the 1989 home visit, when participants were aged 43 years, women were asked by research nurses whether their periods had stopped, the age they stopped and whether the reason for this was natural menopause, hysterectomy or hysterectomy plus oophorectomy.

In each of the 'Women's Health in the Middle Years' postal questionnaires between 1993 and 2000, inclusive, and in 2003, women were asked whether they had undergone any one of the following five procedures: hysterectomy and bilateral oophorectomy; hysterectomy only; hysterectomy and unilateral oophorectomy; bilateral oophorectomy; unilateral oophorectomy and if they had, the month and year or their age in years at the time of this. In the first of these questionnaires, in 1993, women were asked to report if they had ever undergone any one of these procedures, in all following years up to 2000 whether they had undergone a procedure in the previous year and in 2003 whether they had undergone any one of the procedures since 1999. During the 1999 home visit women who had not responded regularly to the 'Women's Health in the Middle Years' questionnaire were asked, in a self-completion questionnaire, whether they had ever undergone any one of the five procedures and the timing of this.

The information collected at these different points was combined. Previous analyses of hysterectomy in the NSHD have used data on hysterectomy up to age 52 years.[80;81] In this thesis all hysterectomy variables have been updated to include hysterectomies reported up to age 57 years. When combining the data from the different data collection points, information from the postal questionnaires and 1999 home visit was taken in preference to the 1989 home visit information given this earlier data collection was less detailed. Where there were differences in the information provided by women in different years an order of preference was established to ensure these were dealt with in a standard way. Where women reported more than one of the five operations and this was compatible e.g. a hysterectomy at one time and a bilateral oophorectomy at another time, the women were coded as having had the combined operation e.g. hysterectomy and bilateral oophorectomy and allocated the date of procedure of the hysterectomy. The end result is that each woman who has responded since 1989 has been coded as having reported one of the five operations or not using a 6 category variable (no hysterectomy or oophorectomy; hysterectomy only; hysterectomy with bilateral oophorectomy; hysterectomy with unilateral oophorectomy;

bilateral oophorectomy; unilateral oophorectomy) and if they have had one of these operations, coded with an age in years and months since birth at the time of their procedure.

2.3.2.2 Descriptive analyses of hysterectomy status

Four hundred and three women (22.4%) in the NSHD reported having undergone a hysterectomy with or without oophorectomy by age 57 years (see table 2.2). Of these women, 5 did not report a date of procedure. Rates of hysterectomy began to increase when women were in their mid-30s reaching a peak when women were in their late 40s before beginning to decline when women reached their early 50s. Figure 2.4 shows that hysterectomy in the NSHD was approximately normally distributed by age. The overall level of hysterectomy reported and the distribution of hysterectomy by age is similar to that seen in other British cohorts of similar age[1;3] suggesting that the data on the timings of hysterectomy are likely to be valid.

2.3.2.3 Ascertainment of reason for hysterectomy

Given both the pathways to hysterectomy and the outcomes of hysterectomy may depend on the reason for the procedure it was considered important to ascertain this information for the women who had undergone hysterectomies in the NSHD.

Where possible this information was taken from hospital records. To obtain information from hospital records cohort members were asked during home visits in adulthood to detail any hospital admissions. From this information, where consent was given, hospitals were contacted to verify these reports and asked to provide details from their records of the admissions. Procedures admitted for and the reasons for these were coded using Office of Population Censuses and Surveys (OPCS) and International Classification of Diseases (10^{th} revision)[82] codes, respectively, by a research nurse. Existing variables coding reasons for hysterectomies performed up to age 43 years were updated to include information from hospital records up to age 53 years. Of the 403 women who underwent hysterectomy 150 were coded as having an unknown reason for hysterectomy when all hospital record data were considered. Information was missing because not all women who had had a hysterectomy participated in the data collections during which permission was gained to access hospital records, not all women who participated in the relevant data collections consented to the hospitals being contacted, some hospitals contacted did not return any information and some women had their hysterectomies after 1999 when hospital records were last obtained.

To improve the completeness of this information a self-completion postal questionnaire was designed and sent in 2005 to women who had undergone hysterectomy.

In designing this questionnaire, the format used for the 'Women's Health in Middle Years' questionnaires which the cohort members were already familiar with was used. As evidence from a systematic review suggests closed-response questions and shorter questionnaires improve response rates to postal questionnaires[83] a 3-page questionnaire in which the majority of questions had a closed-response was used (see appendix 1 for covering letter and questionnaire). The list of reasons for hysterectomy included in the questionnaire was selected based on consultation with Margaret Rees (Reader in Reproductive Medicine and Honorary Consultant in Medical Gynaecology) and Ian MacKenzie (Consultant Obstetrician and Gynaecologist) about the most frequently reported reasons for hysterectomy and the terminology used by doctors when speaking to their patients about these.

Although information on reason for hysterectomy was missing for only 150 women, so that the self-reported reasons for hysterectomy could be validated all women who had had a hysterectomy were eligible to be sent a questionnaire. Of the 403 women coded as having had a hysterectomy, by August 2005 15 had died, 3 had permanently refused to participate and 11 were lost. On 31st August 2005, 374 women were sent a questionnaire with a covering letter and postage-paid reply envelope. To increase the response rate the 104 women who had not responded to the first questionnaire mailing by the 10th October 2005 were sent a second questionnaire package. Ethical approval was received from the Joint UCL/UCLH Committees on the Ethics of Human Research (Committee A) as an extension to the previously approved study 'MRC's National Survey of Health and Development: Follow-up postal questionnaire on women's health' ref 93/0057.

Of the 374 women sent a questionnaire, 322 (86.1%) completed and returned it and a further 6 (1.6%) did not receive the questionnaire as they were returned undelivered.

Reason for hysterectomy, time since hysterectomy, adult occupational class of self and head of household, parity, age at menarche and BMI at ages 43 and 53 years did not significantly predict response to the questionnaire mailing. There was a gradient in response by educational level with 100% of women with a degree or higher returning their questionnaire compared to 80.6% of women with no qualifications but this was only on the borderline of conventional statistical significance ($p=0.08$).

All the data received was entered into a database. Checks were then performed to ensure the data had been entered and converted into variables for use in analyses without errors. This included comparing the variables created on the computer with the paper copies of the questionnaire for 10% of the responding sample.

The validity of the self-reported reasons was tested by comparing these self-reported reasons with the reasons ascertained from hospital records where both were available. Of the 201 women with reasons for hysterectomy recorded by both methods, 128 (63.7%) had self-reported reasons which were in agreement with their hospital record assigned reason (see table 2.3), $\kappa=0.52$, $p<0.0001$ which suggests agreement was moderate.[84] This comparison allowed women to be classified as being in agreement if they had answered 'other' in 2005 and reported in the open space provided a reason in agreement with their hospital record reason or if they had self-reported more than one main reason in 2005 and one of these reasons was in agreement with the main reason assigned from hospital records. Where there was not agreement this could often be explained by the fact that the two conflicting reasons shared common symptoms or one reason was a common symptom of the other, for example, 20.6% of women whose hospital record stated they had a hysterectomy for fibroids self-reported that their hysterectomy was performed for menstrual disorders, a common symptom of fibroids.

As shown in table 2.3, the level of agreement varied by reason for hysterectomy, for example, 94.74% of women whose hospital record reported prolapse as the reason for hysterectomy also self-reported this whereas only 42.86% of women whose hospital record reported endometriosis self-reported this. This variation was significant ($p<0.001$). The only other factor which significantly predicted agreement was adult head of household occupational class ($p=0.007$) with women of lower occupational class less likely to self-report reasons in agreement with their hospital record than women of higher occupational class. Time since hysterectomy, educational level, own adult occupational class, parity, age at menarche and BMI at ages 43 and 53 years did not significantly predict agreement.

Once satisfied that the self-reported reasons were valid and that response and agreement were not significantly predicted by a range of factors, which could have introduced bias, the self-reported reasons for hysterectomy were combined with the hospital records information, taking the information from the hospital records in preference to the self-reported reason where both were available.

2.3.2.4 Descriptive analyses of reason for hysterectomy

When all information was combined the most common main reason for hysterectomy in the NSHD was fibroids with 123 (30.5%) hysterectomies performed for this reason, the next most common reason was menstrual disorders (n=116, 28.8%) followed by prolapse (n=38, 9.4%). There were 28 (7.0%) hysterectomies performed for cancer, 26 (6.5%) for endometriosis and 36 (8.9%) for other known reasons. Only 36 (8.9%) hysterectomies were performed for unknown reasons.

Reasons for hysterectomy varied significantly by category of age at hysterectomy ($p<0.001$) (see figure 2.5). Menstrual disorders were the most common reason for hysterectomies performed before age 45 years whereas fibroids were the most common reason for hysterectomies performed from age 45 years onwards. The proportion of hysterectomies performed for prolapse increased with age while the proportion of hysterectomies performed for cancer did not vary greatly with age.

The distribution of reasons for hysterectomy in the NSHD is similar to that found in other British cohorts,[1;17] taking into account differences in methods used to assign a main reason for the procedure, suggesting that these data are valid.

2.3.2.5 Ascertainment of route of hysterectomy

The uterus can be surgically removed via an incision in the abdomen, vaginally or using laparoscopic techniques[11] with decisions about which route is used dependent on surgeon's preferences as well as the reason for hysterectomy and other factors.[85-87] The consequences of hysterectomy may vary dependent on the route of procedure. To ascertain the route of hysterectomy women were asked in the 'Women's Health in the Middle Years' postal questionnaires sent between 1997 and 2000, inclusive, and in the reasons for hysterectomy questionnaire sent in 2005, to report whether they had undergone an abdominal, vaginal, laparoscopic or unknown type of hysterectomy. The information from the different data collections was combined.

2.3.2.6 Descriptive analyses of route of hysterectomy

The majority of women in the NSHD (n=281, 69.7%) had undergone abdominal hysterectomies, 72 (17.9%) had undergone vaginal hysterectomies and 2 (0.5%) had undergone laparoscopic procedures. This ratio of 3.9:1 abdominal to vaginal hysterectomies is similar to that found in other studies,[17;88] suggesting that this measure is valid. 11.9% of women who had undergone hysterectomy had an unknown route of procedure. Nearly half of all vaginal hysterectomies (n=33, 45.8%) were performed for prolapse, which is what would be expected as prolapse is one of the main indications for vaginal hysterectomy.[88]

2.3.2.7 Ascertainment of menopausal status at time of hysterectomy

Women's menopausal status at the time of hysterectomy may influence the effect of hysterectomy on subsequent health. Menopausal status was ascertained from responses to questions asked in all the 'Women's Health in the Middle Years' postal questionnaires with natural menopause defined as at least 12 months without menstruation in the absence of surgery or other medical treatments including HRT use.

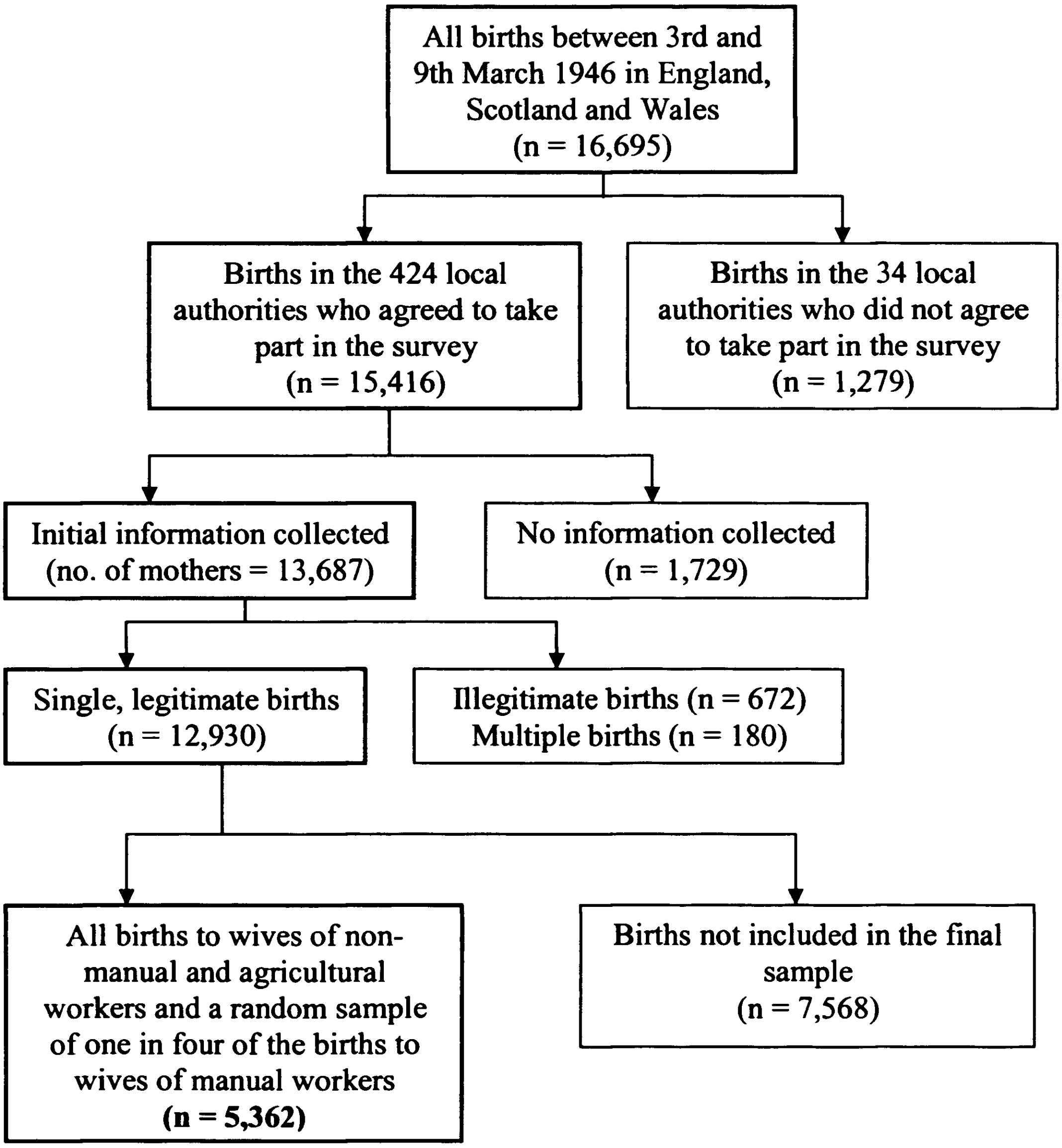
2.3.2.8 Descriptive analyses of menopausal status at time of hysterectomy

Of the 398 with a known date of hysterectomy only 17 had undergone their procedure after a natural menopause. This would be expected given most gynaecological symptoms are no longer experienced after a natural menopause is reached.

2.3.2.9 Other variables used in analyses

The dataset and main variables for use in analyses have been described above. The explanatory variables used in chapters 4 to 7 and the outcome variables used in chapters 9 to 11 are described in subsequent chapters as are methods of analysis.

Figure 2.1: Flow diagram to show how the original NSHD sample was achieved



Person surveyed	Year	Age (years)	Method of data collection
Mother	1946	0	
Mother	1948	2	Home visit by health visitor
Mother and child	1950	4	Home visit by health visitor
Mother and child	1952	6	School Dr at school
Mother and child	1953	7	School nurse or health visitor at school
Mother and child	1954	8	School nurse/health visitor and teacher at school
Mother and child	1955	9	School nurse/health visitor and teacher at school
Child	1956	10	Teacher at school
Mother and child	1957	11	School nurse/health visitor/ Dr and teacher at school
Child	1959	13	Teacher at school
Mother and child	1961	15	School nurse/health visitor and teacher at school
No survey	1962	16	No survey – Annual birthday cards sent from this year on
All cohort members; Mothers of first born	1965	19	Home visit by health visitor; Home visit by interviewer
All cohort members; Mothers of first born	1966	20	Postal questionnaire; Home visit by interviewer
Mothers of first born	1967	21	Home visit by interviewer
All cohort members; Mothers of first born	1968	22	Postal questionnaire; Home visit by interviewer
All cohort members; Mothers of first born	1969	23	Postal questionnaire; Home visit by interviewer
Mothers of first born	1970	24	Home visit by interviewer
All cohort members; Mothers of first born	1971	25	Postal questionnaire; Home visit by interviewer
All cohort members	1972	26	Home visit by interviewer
All cohort members	1977	31	Postal questionnaire
All cohort members	1982	36	Home visit by research nurse
All cohort members	1989	43	Home visit by research nurse
Women	1993	47	Postal questionnaire
Women	1994	48	Postal questionnaire
Women	1995	49	Postal questionnaire
Women	1996	50	Postal questionnaire
Women	1997	51	Postal questionnaire
Women	1998	52	Postal questionnaire
Women; All cohort members	1999	53	Postal questionnaire; Home visit by research nurse
Women	2000	54	Postal questionnaire
Women	2003	57	Postal questionnaire
Hysterectomised women	2005	59	Postal questionnaire

Figure 2.2: Timeline of data collection points **Adapted from Wadsworth et al, 2003[76]**

Figure 2.3: How the sample for the main analyses in this thesis was achieved

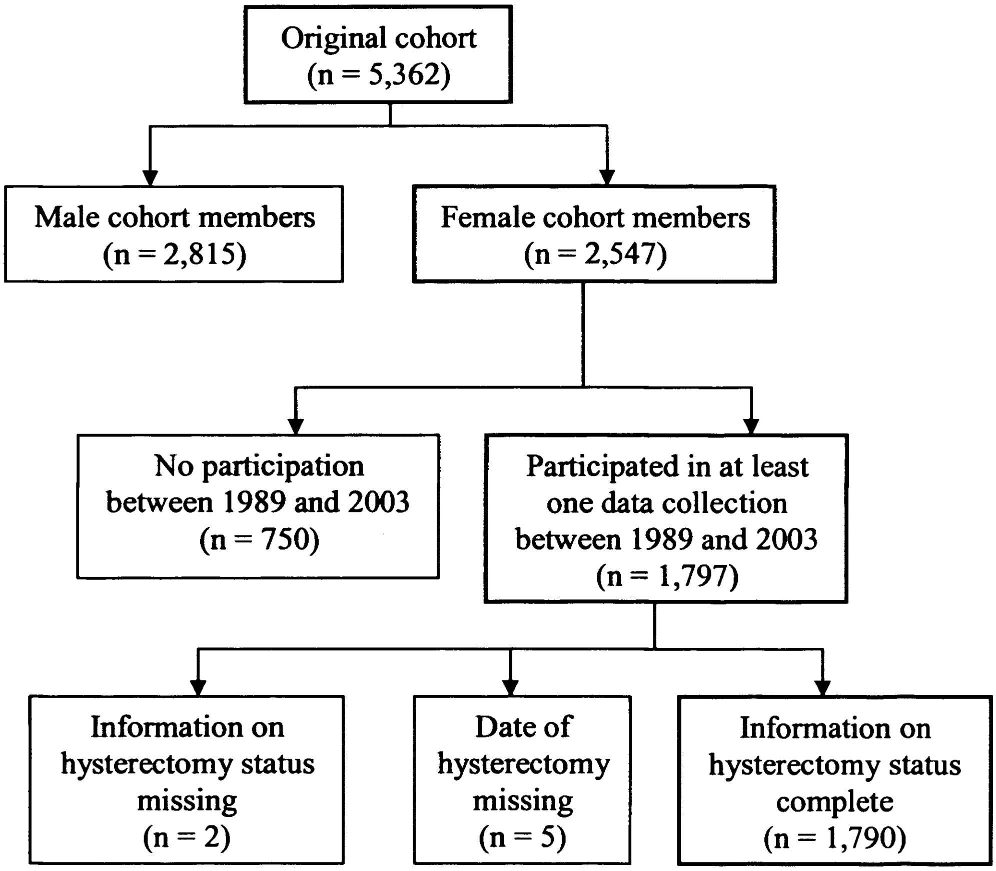


Figure 2.4: Distribution of hysterectomy (with or without oophorectomy) by age in the NSHD (N=398)

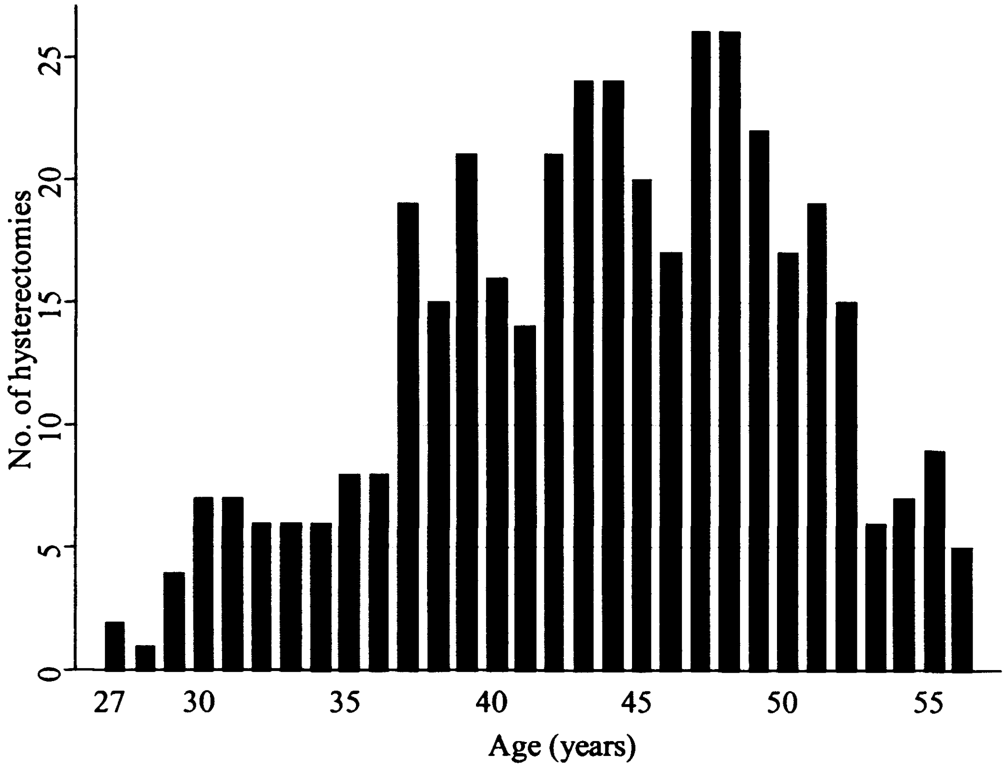


Figure 2.5: Distribution of reasons for hysterectomy by age at hysterectomy in the NSHD (N=398)

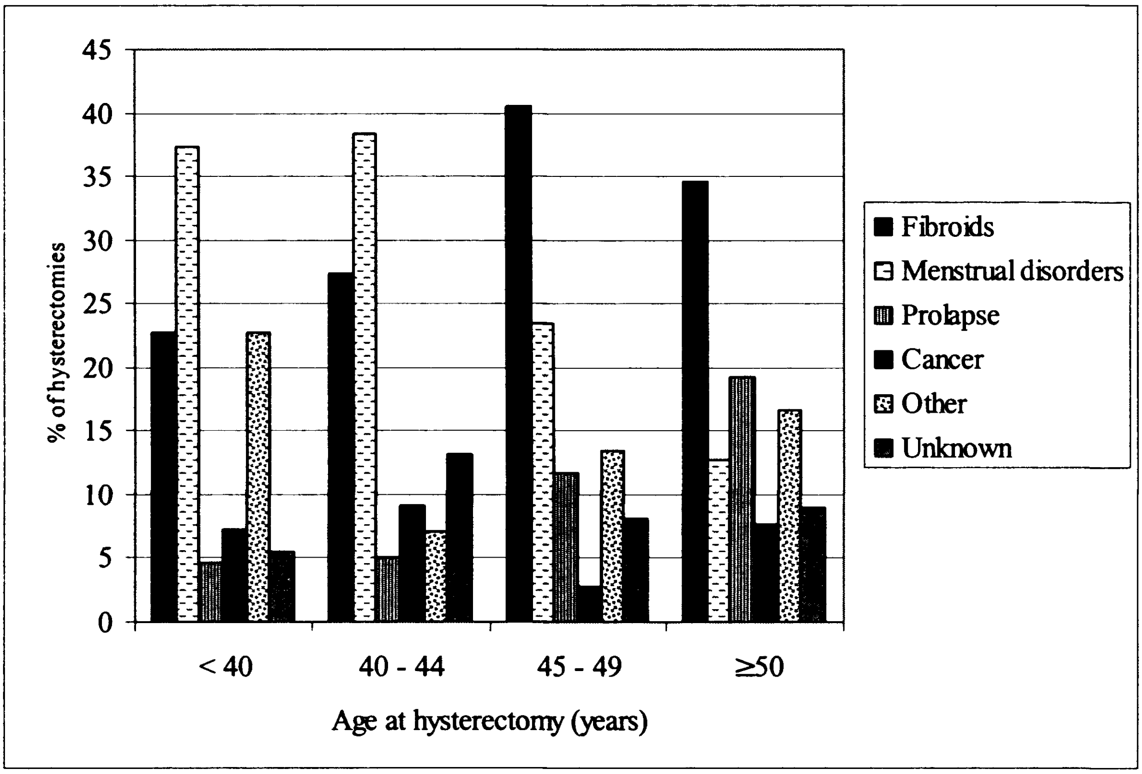


Table 2.1: Reasons for loss of contact with female members of the NSHD at important data collection points

Data collection point	Age (years)	Dead	Abroad	Permanent refusal	Untraced	Participated	Response % of original cohort[a]	Response % of eligible women[b]
1989 home visit	43	147	276	296	101	1628	63.92	94.27
1999 home visit	53	196	262	309	105	1520	59.68	90.75
'Women's Health in the Middle Years' postal questionnaire	47 - 54 and 57	154	232	296	87	1656	65.02	93.14

[a] Denominator is the total number of females in original cohort (n = 2,547)
[b] Denominator excludes women who were dead, abroad, a permanent refusal or untraced

Table 2.2: Number of hysterectomies and oophorectomies reported in the NSHD up to age 57 years

Type of procedure	No. of women	% of women
None	1,362	75.79
Hysterectomy and bilateral oophorectomy	167	9.29
Hysterectomy and unilateral oophorectomy	50	2.78
Hysterectomy only	186	10.35
Bilateral oophorectomy	4	0.22
Unilateral oophorectomy	26	1.45
Missing	2	0.11
Total	**1,797**	**100**

Table 2.3: Comparison of reason for hysterectomy assigned by hospital record and reason self-reported in 2005 questionnaire in the NSHD (N=201)

Reason for hysterectomy self-reported in 2005	Reason for hysterectomy from hospital records (N (column %))												Total
	1	2	3	4	5	6	7	8	9	10	11	12	
1	18 (94.74)	0	0	0	1	1	0	0	1	0	0	0	**21**
2	0	6 (42.86)	1	0	2	1	0	0	0	0	0	1	**11**
3	0	0	0 (0)	0	0	0	0	0	0	0	0	0	**0**
4	0	0	0	0 (0)	0	0	0	0	0	0	0	0	**0**
5	1	5	1	1	43 (67.19)	14	1	0	0	1	0	2	**69**
6	0	2	0	0	11	47 (69.12)	2	1	1	0	0	1	**65**
7	0	0	0	0	0	0	10 (66.67)	0	0	0	0	0	**10**
8	0	0	0	0	0	0	0	0 (0)	0	0	0	0	**0**
9	0	0	0	0	1	0	0	0	0 (0)	0	0	0	**1**
10	0	1	0	0	1	1	2	1	0	4 (80.00)	3	0	**13**
11	0	0	0	0	0	0	0	0	0	0	0 (0)	0	**0**
12	0	0	0	0	0	0	0	0	0	0	0	0 (0)	**0**
13	0	0	0	0	5	2	0	1	1	0	0	0	**9**
14	0	0	0	0	0	2	0	0	0	0	0	0	**2**
Total	**19**	**14**	**2**	**1**	**64**	**68**	**15**	**3**	**3**	**5**	**3**	**4**	**201**

Note: The figures shaded are those where the two measures are in agreement

Reasons for hysterectomy: 1=Prolapse; 2=Endometriosis; 3=Disorders of the uterus; 4=Genital organ pain; 5=Menstrual disorders; 6=Fibroids; 7=Cancer, invasive and pre-invasive; 8=Neoplasm unspecified; 9=Inflammatory disease of the female pelvic organs; 10=Non-inflammatory disorders of the female genital organs; 11=Benign neoplasms; 12=Fibroids and endometriosis; 13=Other; 14=Multiple reasons

Chapter 3: An introduction to the predictors of hysterectomy

3.1 Introduction

In this section of the thesis a number of potential predictors of hysterectomy are examined. This chapter provides an introduction to the study of predictors of hysterectomy and a summary of what follows in the subsequent four chapters. The following three each investigate a different set of potential predictors of hysterectomy and the fourth examines the inter-relationships between the different predictors identified.

3.2 Trends in hysterectomy rates over time and place

In considering those factors which may predict risk of hysterectomy, it is necessary to consider the variation in hysterectomy rates which have been found over time and place as these provide clues as to how hysterectomy risk is determined.

3.2.1 Trends in hysterectomy rates over time in the UK

Analyses of routinely collected data[3;4;16;89;90] and from a cohort study[1] provide empirical evidence of overall trends in hysterectomy rates over the second half of the twentieth century in the UK. Scottish Morbidity Record and Hospital In-patient Enquiry data were used by Teo[89] to study the trends in rates of hysterectomy performed on the NHS between 1961 and 1984 in Scotland and between 1965 and 1981 in England and Wales. Teo found that hysterectomy rates fluctuated over time but there was an overall increase towards higher rates at later dates in both populations – rates increased from approximately 125 to 250 per 100,000 women in Scotland between 1960 and 1985 and from approximately 210 to 250 per 100,000 women in England and Wales between 1965 and 1981. Rates of hysterectomy by reason were also examined using the Scottish data and this showed that while rates of hysterectomy for most reasons had remained relatively stable over time, rates of hysterectomy for menstrual disorders had doubled between 1960 and 1985. Another study[3] which analysed NHS (Hospital In-Patient Enquiry and Hospital Episode Statistics) and private hospital data for England and Wales, covering a wider time period, from 1961 until 1995, found similar results although estimates of rates were slightly higher. As shown in figure 3.1, these analyses suggest that hysterectomy rates in England and Wales increased from 1961 until 1988, declined between 1988 and 1991 and then remained stable from 1991 to 1995. These analyses found that increases between 1968 and 1974 were due to increased rates among women aged under 40 years with the increases after 1984 seen across all age groups. Similar results were also found in less detailed studies of routinely collected data.[4;16;90]

Using data from an Oxford-based cohort study, Vessey and colleagues,[1] examined changes in age-specific rates of hysterectomy over time. Rates of hysterectomy performed on women between the ages of 30 and 40 years increased between 1974 and 1989, remained relatively stable in women aged 40 to 44 years and declined slightly in women aged 45 years and over.

More than one study suggests that the increase in rates seen in the latter half of the twentieth century up until the late 1980s was due in part to an increase in the number of hysterectomies performed on women aged less than 40 years. This could be because of the growing acceptability of menstrual disorders, the most common gynaecological condition in women of that age group, as an appropriate reason for hysterectomy or alternatively or, in addition, because of an increasing prevalence of menstrual disorders and other gynaecological conditions in younger women over time. However, whether there have been changes in the levels of gynaecological morbidity over time is difficult to assess as there is a paucity of data on trends in gynaecological conditions, possibly because such data are difficult to collect. Changes in the age structure of the population, in parity, timing of childbirth, obesity levels and exogenous hormone (oral contraceptives and hormone replacement therapy) use over time would be expected to have impacted on the incidence of gynaecological conditions in ways which could have affected hysterectomy rates.

In addition to changes in both the conditions considered appropriate for treatment with hysterectomy and attitudes to hysterectomy over time, discussed in chapter 1 and, changes in the prevalence of gynaecological morbidity, another possible explanation of changes in hysterectomy rates over time are changes in the availability of alternative treatments. Many recent studies have aimed to examine the impact on hysterectomy rates of the introduction in the late 1980s and early 1990s of a number of alternative treatments for gynaecological conditions including endometrial ablation, uterine artery embolisation and levonorgestrel-releasing intrauterine devices. These are seen by many as viable and acceptable alternatives to hysterectomy[21;91-95] and hence were expected to cause an immediate decline in hysterectomy rates when introduced. Analysis of Mersey Region hospital activity data showed that between 1991 and 1993 the number of hysterectomies performed had increased at the same time as the number of endometrial ablations performed also increased rather than decreasing as expected.[96] The same was found by Coulter[97] in an analysis of Oxford Regional Health Authority data over the same time period. However, Armatage and colleagues,[98] in analyses of data from the Liverpool Women's Hospital collected between 1989 and 1993, found evidence that the rates of hysterectomy for conditions which can now be treated with endometrial resection were declining. In a later article, Bridgman and Dunn[99] assessed this trend in NHS hospitals in England between 1989 and 1996. They found that rates of hysterectomy for dysfunctional uterine bleeding had not been greatly affected by the introduction of endometrial ablation and suggested, as some early reports had hinted, that there had been a lowering of the threshold for all types of operation for this gynaecological condition. Another study in the UK has also failed to find a decline in hysterectomy rates over time despite the introduction of alternatives,[17] a finding mirrored in other countries including the USA.[100] However, the most recently published analysis of trends in hysterectomies in England which used Health Episode Statistics collected between 1989 and 2002-3 suggest that since the mid-1990s there has been a decline in rates of hysterectomy for menstrual disorders which coincides with the introduction of alternative treatments for this condition,[101] a trend also seen in other countries including The Netherlands.[102]

What is clear is that trends in rates of hysterectomy over time are determined by a complex range of factors including changes in those factors discussed above.

3.2.2 Geographical variation in hysterectomy rates

As well as there being variation in hysterectomy rates over time there is also significant variation in hysterectomy rates between places - both countries[4;103-105] and regions within countries.[4;89;106;107] Such variation is found even where populations would be expected to have similar levels of underlying gynaecological morbidity. As an illustration of this variation McPherson[103] presented the annual admission rates for hysterectomy in a wide range of countries in the early 1980s. Rates ranged from 557 per 100,000 in the USA to 48 per 100,000 in Sweden. Similar levels of variation were also found in other studies.[95;105]

Some critics of surgical intervention and its alleged overuse have used the variation in rates between populations in different times and places that would be expected to have similar levels of gynaecological morbidity as evidence that procedures are being performed unnecessarily. Most recently the UK's Chief Medical Officer has used the variation in hysterectomy rates and variation in the rates of decline in hysterectomy rates between regions within the UK to argue that the service provided by the NHS is inequitable and that the procedure may be being overused in some areas.[107] However, as Schact and Pemberton[105] argue, while it could suggest overuse of surgery in areas and time periods with relatively high rates this variation could conversely imply that populations with relatively low rates are not receiving enough surgery, an argument also proposed by Coulter and colleagues.[4]

3.3 Determinants of a surgical rate

While the study of the predictors of hysterectomy may initially appear straightforward given hysterectomy is a clearly defined, once in a lifetime event, this is not the case. As alluded to in the description of the variation in rates of hysterectomy above, a woman's risk of hysterectomy is determined by a complex interplay of factors which vary over time and place. In considering those factors which influence surgical rates Coulter and colleagues[4] presented a diagram of the different factors they considered important, reproduced in figure 3.2. This suggests that the factors which will predict hysterectomy rates include not only those biological and social factors which influence medical need for surgery (i.e. the development and severity of gynaecological conditions) but also those which influence, what Coulter and colleagues term, supply and demand factors. Any one predictor may be expected to have differing levels of effect on hysterectomy risk over time and place dependent on whether it operates mainly through an association with medical need or supply and demand factors. This is because there will be changes in the relative level of contribution of medical need and supply and demand factors in determining hysterectomy risk over time and place and by the gynaecological condition requiring treatment.

Further evidence of the complexity of the process leading to hysterectomy is demonstrated in figure 3.3. Devised by Wu and colleagues[108] following interviews with women who had undergone hysterectomy for fibroids this shows the options a woman has to consider when deciding whether to undergo hysterectomy. This model proposes that unless the gynaecological condition from which a woman is suffering is potentially life-threatening there are several stages of decisions which she will need to make before she chooses whether to have a hysterectomy. This supports the idea that 'demand factors' as well as medical need are important in determining risk of hysterectomy. It seems likely that each decision will be influenced by various social and biological factors including a woman's age, her experience of symptoms, the amount of information provided by doctors and other sources about alternatives and the consequences of the procedure and past experiences of medical care. Although ideally a woman should be able to make fully informed decisions at each stage of the process research suggests that women are not always adequately informed and feel that they are not appropriately involved in the decision process leading to hysterectomy[109;110] confirming that other demand and supply factors outside the woman's control must also operate to influence hysterectomy risk.

3.4 Findings from published studies of the predictors of hysterectomy

Published studies have examined a wide range of potential predictors of hysterectomy. Table 3.1 summarises those factors which have been investigated (it should be noted that inclusion in this table does not mean that any particular factor was found to be significantly associated with hysterectomy when investigated). These include sociodemographic, reproductive and lifestyle factors, prior gynaecological history and genetic factors. Although not fully exhaustive this table provides an indication of the variety of different factors which have been investigated. Findings from studies which have examined potential predictors selected for further study in this thesis are reviewed in more detail in subsequent chapters.

In summary, many existing studies have examined a range of potential predictors without providing good justification for their selection. The methods which have been used have often not been satisfactory because: they have not enabled the establishment of a clear temporal relationship between the potential predictor and hysterectomy; have not tested or been able to test for changes in the association between the predictor and risk of hysterectomy by age at hysterectomy; have not assessed whether the association differs by reason for hysterectomy; do not consider the inter-relationship between different predictors; and have not considered the role of different factors acting across life.

Another criticism of existing studies is that where associations have been found there is often no or very little attempt to explain the findings and to suggest how the predictors could be acting to influence hysterectomy risk.

3.5 Pathways between predictors and hysterectomy

A framework proposed by Hardy and Kuh,[69] see figure 3.4, demonstrates that there are a wide range of factors which could plausibly influence the risk of hysterectomy either directly or through their influence on other factors. It also shows that there are likely to be factors acting to influence hysterectomy risk at all stages of life rather than only in adulthood. Taking socioeconomic status (SES) as an example, this framework suggests that SES may be influential at different time points across life, acting to influence risk of hysterectomy through any one or more of a number of pathways. This framework suggests that factors which could mediate the relationship between SES and hysterectomy include reproduction and body composition – the timing of childbearing, parity and body composition are all socioeconomically graded[111-113] and these factors may influence risk of developing gynaecological problems and hence medical need for hysterectomy and also influence psycho-social pathways to hysterectomy.

3.6 Benefits of further study

In order to inform the debate about whether hysterectomy is necessary further studies of predictors of hysterectomy are required. As Coulter and colleagues suggest, in discussing how to address concerns about how necessary hysterectomy is,

'The challenge for researchers is to try to identify patterns of variation in order to increase understanding of what is going on, with the eventual aim of improving the targeting of health care resources.'[4] (p.988)

This is also highlighted by Schofield and colleagues,

'Two factors, the elective nature of hysterectomy and the widespread variations in hysterectomy rates, point to the need to investigate more carefully factors which may predict hysterectomy rate and help us to elucidate the appropriateness of this major surgical intervention for women.'[114] (p.157)

In assessing the appropriateness of hysterectomy, it is also necessary to consider the consequences of the procedure i.e. the costs and benefits. As discussed in more detail in chapter 8, in order to appropriately assess the long-term health consequences of hysterectomy it is necessary to adjust for factors from across life that could independently predict both hysterectomy and the health outcome of interest i.e. potential confounders. However, the factors which need to be adjusted for can only be appropriately identified if the life course predictors of hysterectomy as well as those of the health outcome are known. For this reason it is of benefit to define the predictors of hysterectomy within a population.

3.7 The predictors examined in this thesis

It was not possible with only one dataset to examine all potential predictors of hysterectomy satisfactorily and so those most suited to study using a life course approach which it was thought could be most appropriately studied using data from the NSHD were chosen.

Three sets of predictors have therefore been considered in subsequent chapters of this thesis: indicators of socioeconomic position (SEP) at time points across life; lifetime body weight; and reproductive characteristics. The full justification for assessing each of these three sets of factors and the specific objectives to be addressed are provided in the relevant chapters which follow. In summary, as demonstrated in the framework for these chapters shown in figure 3.5, all three sets of factors could be acting at different stages across life to influence hysterectomy risk, either through their influence on medical need or supply and demand factors. In the following three chapters, as indicated in figure 3.5, each set of factors has been considered separately and their associations with hysterectomy assessed. In addition, analyses in these chapters have also assessed the independence of each association from the associations between other factors within the same set of predictors and hysterectomy.

Another reason for selecting these three sets of factors is that lifetime SEP, weight and reproductive characteristics are all associated (not apparent in figure 3.5 as the potential lines of association between the different sets of factors have been omitted). It is therefore possible that the association between a predictor from within one set of factors and hysterectomy could be explained by its association with a predictor from within one of the other sets of factors either because it mediates or confounds the association. This has been explored in chapter 7 after the factors which predict hysterectomy within each set of factors have been identified.

Although the framework in figure 3.5 shows all potential predictive factors operating through gynaecological health (medical need) and/or supply/demand factors to influence hysterectomy the information available about the women in the NSHD does not allow direct investigation of these mediating stages. However, by examining not only the associations between each predictor and overall hysterectomy risk but also the associations between each predictor and hysterectomy by reason and, by considering the inter-relationship between the different predictors and their effect on overall hysterectomy risk it has been possible to deduce whether each predictor is more likely to be operating on medical need or supply/demand factors to influence hysterectomy risk and hence elucidate which pathways may be operating between various factors across life and subsequent hysterectomy.

3.8 Methods

To avoid repetition in the next four chapters, the general methods used to examine the predictors of hysterectomy are described below with more specific details provided where necessary in the appropriate chapters.

3.8.1 Study population

The study population used to assess the predictors of hysterectomy consists of all women in the NSHD with valid information on hysterectomy status up to age 57 years and a valid date for hysterectomy if they had undergone this procedure (N=1,790). How this study population was achieved was described in chapter 2.

3.8.2 Main outcome variable

Hysterectomy with or without oophorectomy (method of ascertainment described in chapter 2).

3.8.3 Categorisation of outcome variables

The main outcome in the next four chapters is the binary variable: hysterectomy with or without oophorectomy vs. no hysterectomy.

The association between potential predictors and hysterectomy could vary by reason for hysterectomy, so analyses were also performed which examined the unadjusted associations between predictors and hysterectomy by reason for hysterectomy. For the purposes of these analyses women who had reported undergoing a hysterectomy with or without oophorectomy were grouped into six categories based on their main reason for hysterectomy (method of ascertainment described in chapter 2): fibroids; menstrual disorders; prolapse; cancer; other known reason; unknown reason. The other known reasons category included a range of reasons for hysterectomy which were each reported by so few women that there was insufficient power to consider them in their own individual categories.

In all analyses of the predictors of hysterectomy women who had reported a unilateral or bilateral oophorectomy only were grouped with women who had not reported having had a hysterectomy as they were not expected to differ in important ways from non-hysterectomised women and, when checks were made it was found that the inclusion of these women in the no hysterectomy group did not alter the findings compared to analyses in which they were excluded. No distinction was made between women who had a hysterectomy only and women who had a hysterectomy accompanied by an oophorectomy or between women who had hysterectomies by different routes of procedure (i.e. abdominal, vaginal or laparoscopic). This is because these characteristics were not expected to be influenced by the same factors which predict a woman's risk of hysterectomy - decisions about the route of procedure and whether an oophorectomy is performed concomitantly have been found to depend more on the preferences of the surgeon rather than specific characteristics of the women or their reason for hysterectomy.[85-87;115;116]

3.8.4 Explanatory variables

These and their ascertainment are described in the relevant chapters.

3.8.5 Analyses

Unless otherwise stated, analyses presented in this thesis were performed using STATA version 9.2.

3.8.5.1 Preliminary analyses

After performing a range of checks on the data, the first stage in assessing the association between each potential predictor and hysterectomy was to perform basic comparisons of the distribution of each predictor in the hysterectomised and non-hysterectomised groups. For all continuous predictor variables the mean in the hysterectomised group was compared to the mean in the non-hysterectomised group using t-tests (after first checking that it was appropriate to use t-tests by assessing whether the continuous measures were approximately normally distributed and that the standard deviations in the hysterectomised and non-hysterectomised groups were similar). For all categorical measures chi-squared tests were used to compare the proportions of women who had undergone hysterectomy in each category of the variable. For brevity and because not all women in the NSHD were followed-up to the same age whereby some women may have been misclassified as 'no hysterectomy' in these analyses having had hysterectomy after the point of last contact the results from these analyses are not presented.

3.8.5.2 Survival analyses

As described in chapter 2, in addition to the hysterectomy status of women in the NSHD, the time of hysterectomy was also recorded. To utilise this time to event data and to allow for the fact that not all women in the NSHD for whom hysterectomy status is recorded were followed-up to the most recent data collection point at age 57 years the most appropriate method of analysis to use was survival analysis. Cox's proportional hazards models were used in the analyses presented in the following four chapters. Unless otherwise stated, these survival models were run on the age-time scale with follow-up in months since the cohort members' average age at menarche (age 12.6 years) until hysterectomy. Follow-up times of women who had not had a hysterectomy were censored at the age when they last completed a questionnaire. Assumptions of proportionality were assessed in all models by examination of plots and testing for evidence of an interaction between each predictor and the age-time scale - where there was evidence that these assumptions were violated alternative models were used as described in the relevant chapters where necessary. If predictor variables were ordinal tests for trend were performed and, if they were continuous tests of deviation from linearity were performed.

3.8.5.3 Competing risks analysis

A competing risks framework[117;118] was used to assess whether the association between each potential predictor and subsequent hysterectomy rates differed by reason for hysterectomy. This involved running a separate set of Cox's proportional hazards models for each category of reason for hysterectomy. For example, to test the association between each predictor and hysterectomies for fibroids women with hysterectomies for fibroids were coded as having a positive outcome (i.e. 1) whereas women with hysterectomies for any other reason were coded along with women who had not had a hysterectomy as 0 and their follow-up censored at the time of hysterectomy. This was repeated for each of the six categories of reason for hysterectomy.

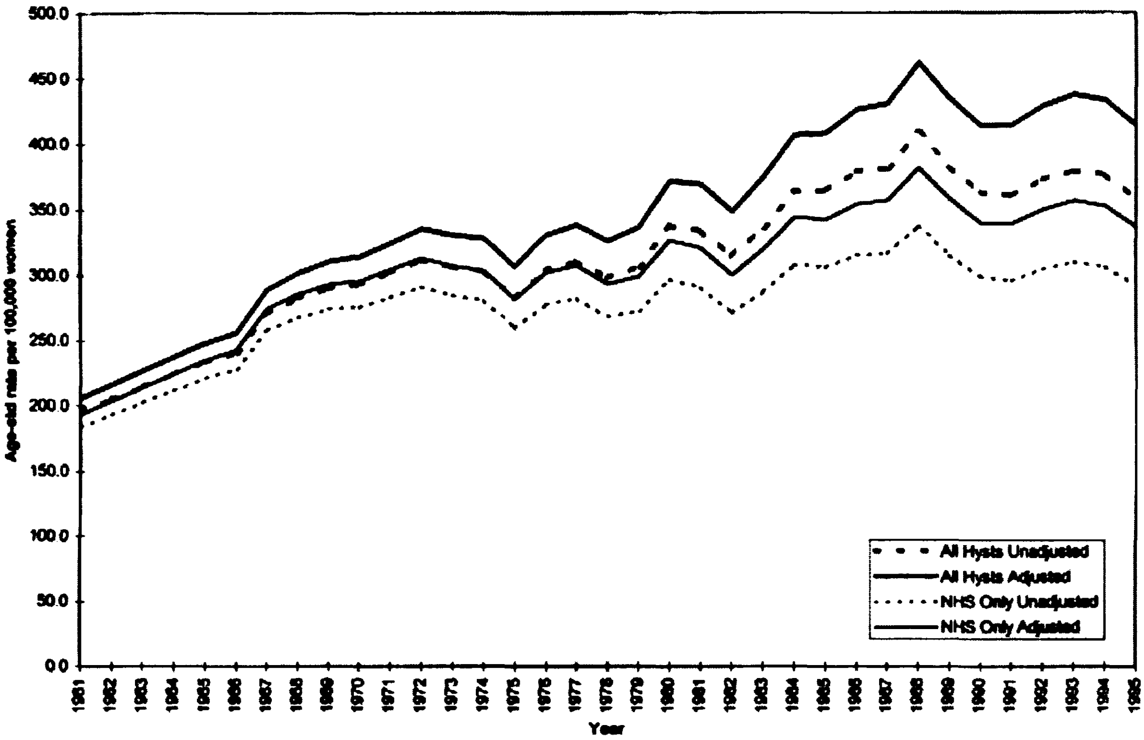
3.8.5.4 Tests of statistical significance

Unless otherwise stated p-values presented in results tables are from likelihood ratio tests comparing a model with the variable of interest included to a comparable model with the variable not included. When assessing the results of analyses, p-values < 0.05 were considered to be statistically significant.

3.8.5.5 Allowing for the stratified sampling procedure

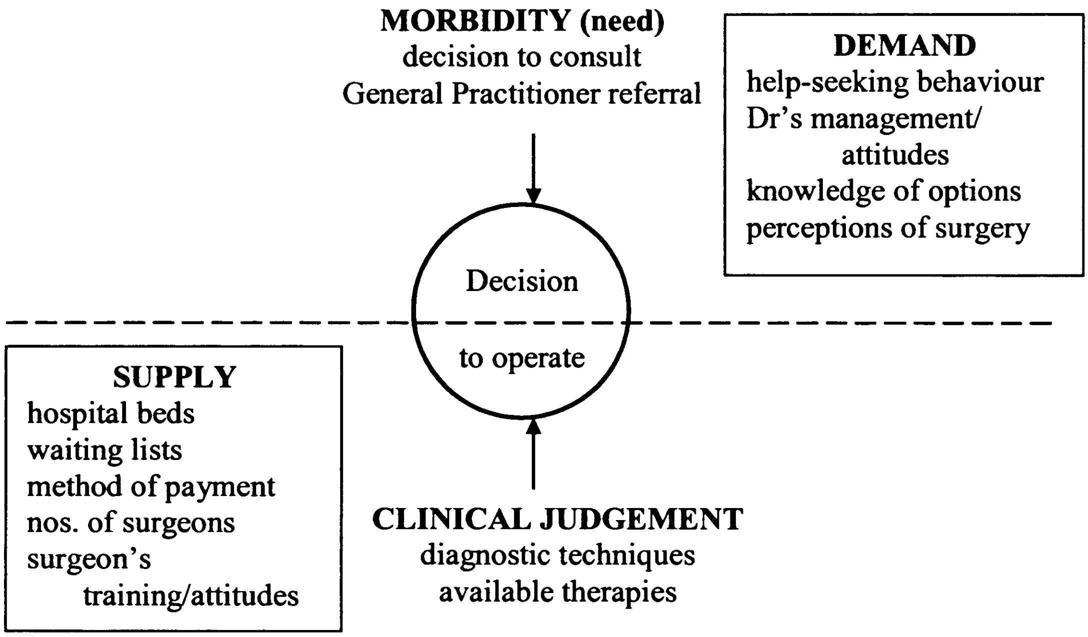
As described in chapter 2, the NSHD is a stratified sample of all legitimate, single births which occurred during one week in March 1946. Analyses can be weighted to allow for this stratification although there is no need to do so if results from weighted analyses are similar to those from unweighted analyses. Results from weighted analyses were compared to results from the equivalent unweighted analyses and as weighting the analyses did not alter the findings the results from unweighted analyses are presented in the four chapters which follow.

Figure 3.1: Age–standardised hysterectomy incidence rates per 100,000 women, 1961–95, England and Wales, (all hysterectomies and NHS only) unadjusted and adjusted for the true population at risk



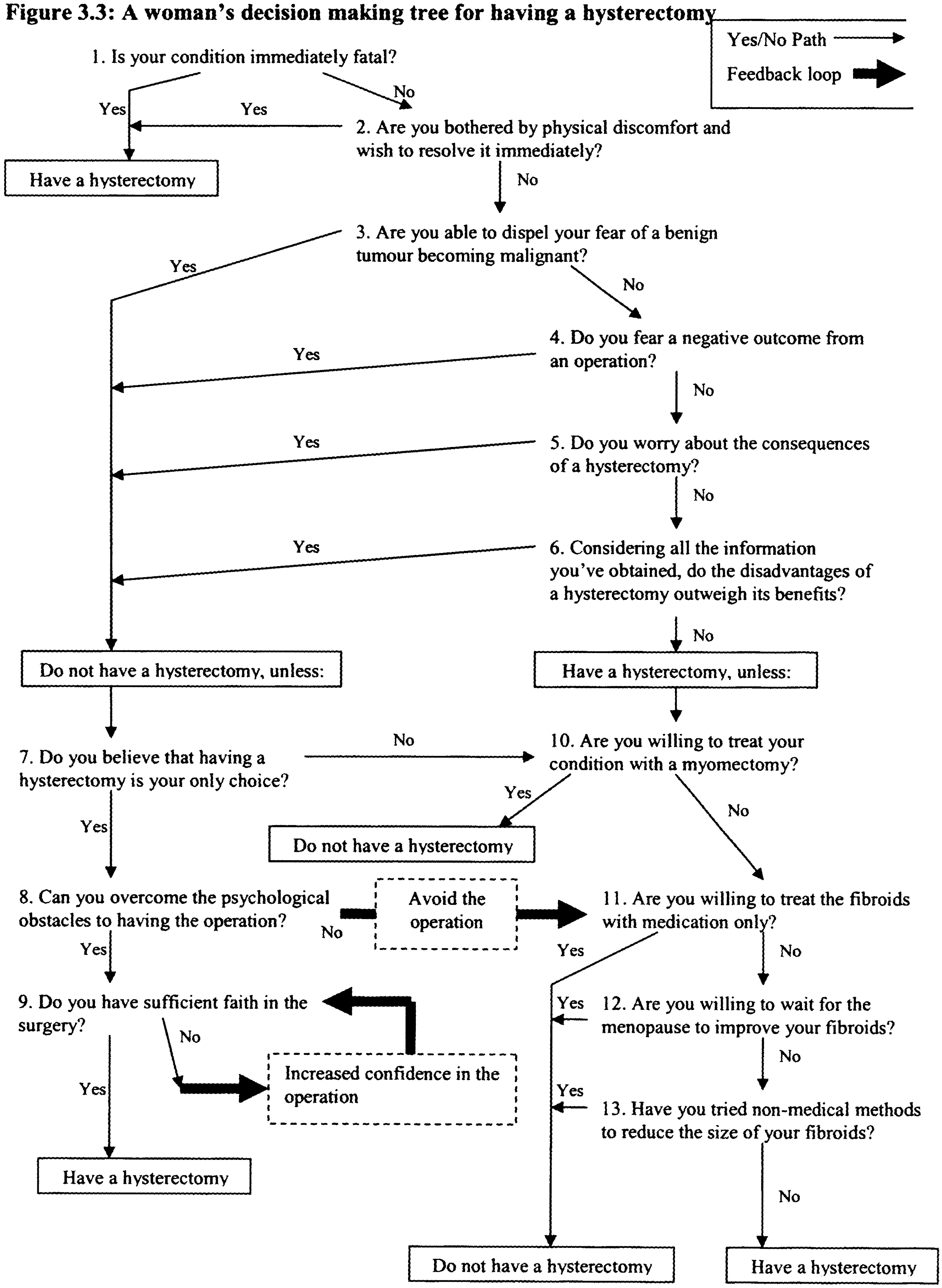
Taken from Redburn and Murphy[3]

Figure 3.2: Determinants of a surgical rate



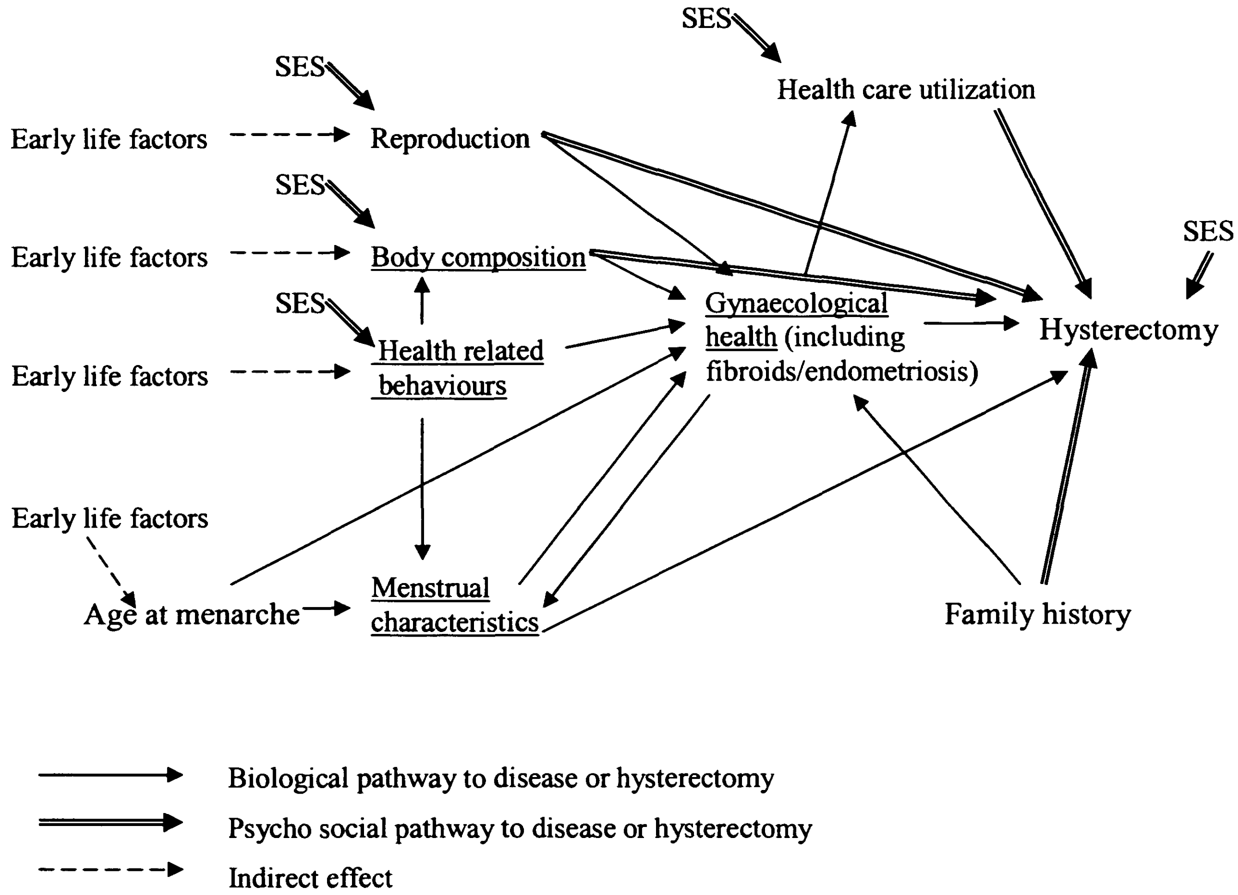
Taken from Coulter, McPherson and Vessey, 1988[4]

Figure 3.3: A woman's decision making tree for having a hysterectomy



Taken from Wu et al, 2005[108]

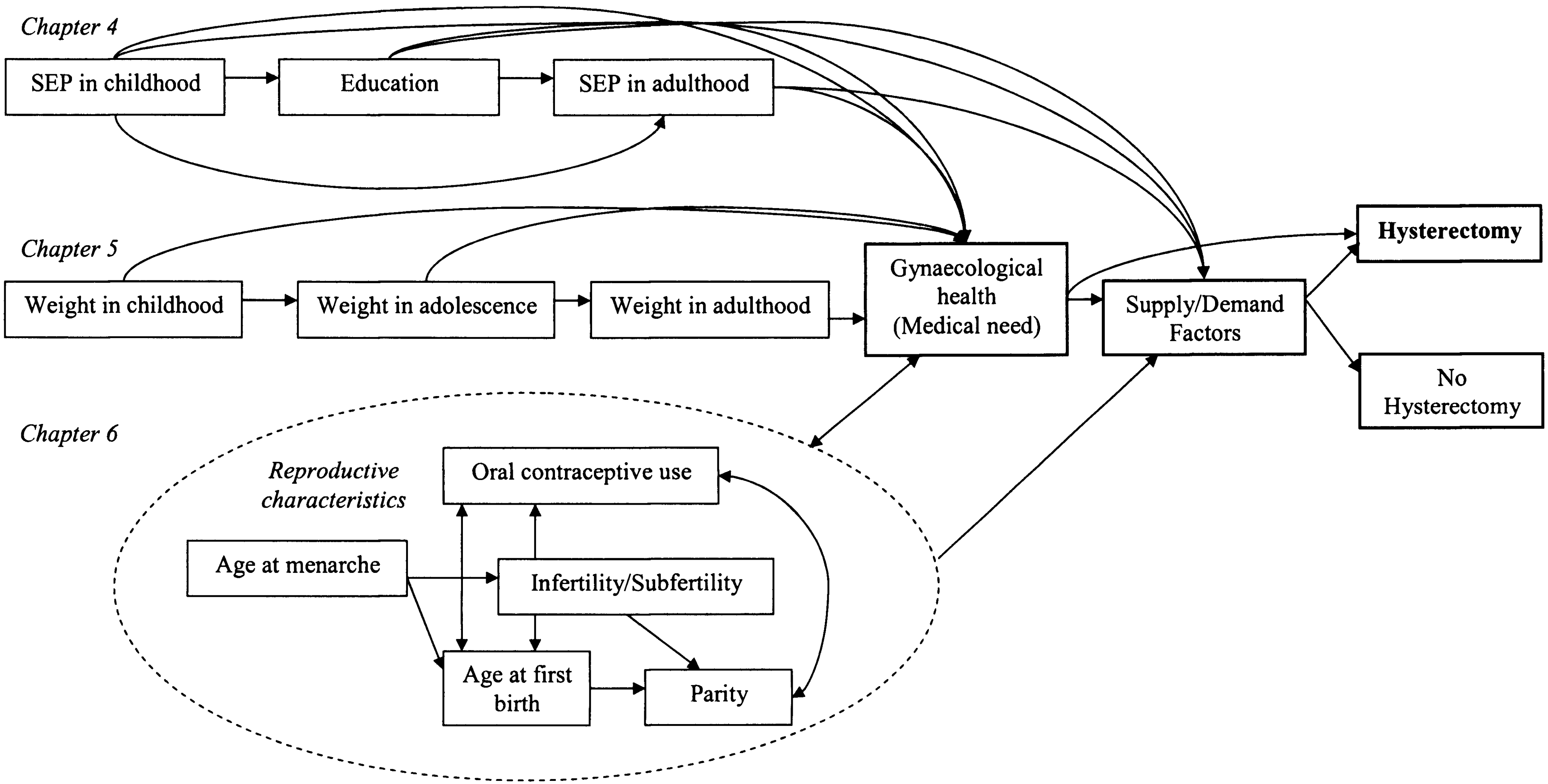
Figure 3.4: Pathways to hysterectomy: a framework



Underlined type represent effects which could be acting across the life course

Taken from Hardy and Kuh, 2002[69]

Figure 3.5: Framework of predictors of hysterectomy examined in this thesis



Please note: only 1 line has been drawn between all reproductive characteristics and gynaecological health and between all reproductive characteristics and supply/demand, this is to simplify the diagram and although all the reproductive characteristics shown could be components of an underlying measure of reproductive function it is also possible that each reproductive characteristic is associated with gynaecological health and/or supply/demand independently of other reproductive characteristics

Table 3.1: Potential predictors of hysterectomy previously investigated

Patient characteristics (Medical need & Demand factors)

Sociodemographic factors
- Age[1;11;119-130]
- Education[80;81;114;119-144]
- Income[121;122;124;129;135;138;139;145;146]
- Occupation[1;80;81;114;119;123;131;133;135;136;138;139;147-149]
- Other measure of socioeconomic position[137;139;141;144;150]
- Ownership of health insurance[141;151]
- Race/Ethnicity[11;119-122;125;137;142;145;152;153]
- Place of residence or birth[114;119;123;124;127]
- Marital status[114;119;120;122;125;126;129;130;141;143]
- Religion[119;125;127]

Lifestyle factors
- Smoking[120;122;124;125;128;129;132;151;153;154]
- Weight/BMI[120;122;124-126;129;130;142;144;153-165]
- Alcohol consumption[124;125;128;142]
- Sedentary lifestyle/Exercise[129;142;154]

Gynaecological factors
- Pre-menstrual symptoms[132]
- Regularity of menstruation[120;122;144]
- Number of prior D & C procedures[128;132]
- Prior sterilisation[119;127;128;141;166]
- Prior gynaecological morbidity[120;128;167]

Genetic factors[162;164;168-170]

Reproductive and Hormonal factors
- Age at menarche[120;125;129;132;151;167]
- Age at first birth[122;125;129;137;144;151;165]
- Parity[1;119;120;122;123;125-130;137;140;141;143;144;151;153;165;167;171]
- History of miscarriage or abortion[119;122;127;130;137;167]
- Problems conceiving[128]
- Use of oral contraceptives or an intrauterine device[119;120;127;130;144;151;167]
- Prior caesarean section[122]
- Use of HRT[124;129;172]

Health seeking behaviours
- Non-gynaecological operations[128;132]
- Use of prescription medicines[132]
- Use of traditional medicines[130]
- Mammography[122;124]
- Number of GP visits[124;149;173]

Health status
- Irritable bowel syndrome[149]
- Hypertension[122;124;129;174;175]
- Diabetes mellitus[122;124]
- Non-gynaecological cancer[122]

Supply factors

Characteristics of doctor
- Sex[176-179]
- Time since training[176;178]
- Density of surgeons[89;176]
- Financial incentives[178]
- Level of surveillance of Dr's practice[180]

Time
- Calendar period[1;119;123;127]

Chapter 4: Socioeconomic position and hysterectomy

Main objective: To investigate whether indicators of socioeconomic position (SEP) from across life are associated with hysterectomy risk.

4.1 Introduction

This chapter focuses on the role of SEP as a predictor of hysterectomy risk. It updates and advances the previous published work which has found inverse associations between indicators of SEP and hysterectomy in the NSHD.[80;81;133] It also compares the associations found in the NSHD with associations found in other British cohorts, born in different decades of the twentieth century. This has allowed the potentially dynamic nature of the association between SEP and hysterectomy over an individual's life and over different historical time periods to be examined.

SEP is increasingly accepted as the most appropriate term for use in epidemiological research which examines socioeconomic differentials in health[181;182] and is defined as,

> 'the social and economic factors that influence what positions individuals or groups hold within the structure of a society.' Galobardes et al, 2006[183] (p. 7)

This construct is not directly measurable and is instead indicated by aggregate variables which are measures of resources and prestige including occupational class, education and income.[181;183] Although a large number of studies[1;80;81;114;119-151;184] have tested the association between at least one indicator of SEP in adulthood and hysterectomy it is still not clear how independently of each other the different indicators of SEP at any one point in life act to influence hysterectomy risk and during which periods of life SEP is most influential.

There are a number of plausible pathways on which indicators of SEP across life could act to influence hysterectomy risk.[69] Indicators of SEP could be associated with hysterectomy risk through their influence on factors which determine levels of medical need for hysterectomy or through their influence on supply and demand factors. Factors associated with SEP and also with hysterectomy risk include supply and demand factors such as:

considered value of surgery;[147] access to health care and information;[114;119;137-139;145] health care utilisation;[119;121;151;185] frequency of gynaecological examinations;[121;139;150] stage of gynaecological disease at the time of presentation to a doctor;[120;121]Dr-patient relationships;[114;119;126;127;133;134;136;139] preferred forms of medical treatment;[120;127;133] and level of choice in health decisions[127] and, factors influencing medical need such as: risk of developing gynaecological conditions;[81;122;135;138] age at childbearing;[114] parity; reproductive organ development and health;[80;136;139] obesity;[186] and health behaviours.

While the associations between each different indicator of SEP and hysterectomy may be explained by one common pathway it is possible that the reasons for finding associations between each indicator of SEP and hysterectomy differ. Different indicators of SEP are correlated[183;187] because they all measure aspects of SEP which are related, however, there are aspects of each indicator which are different from others. This is true not only for different indicators of SEP measured at the same point in life but for the same indicators of SEP measured at different time points across life.

Many of the possible explanations of socioeconomic variation in hysterectomy risk suggest socioeconomic variation in supply and demand factors rather than in medical need. If this is true it would suggest inequity in treatment of women by SEP with women of lower SEP, given most associations found are inverse, being at greater risk of hysterectomy despite possibly having no greater medical need. This has important implications and, therefore, attempts to uncover if this is true through identification of the most influential indicators of SEP would be beneficial. Further, by acquiring a better understanding of the relationship between SEP and hysterectomy, it may be possible to gain an insight into the wider issue of socioeconomic variation in health care access and utilisation.

In creating a framework of those factors across life which are important predictors of hysterectomy, examining the association with lifetime SEP is important - if there are socioeconomic gradients it implicates other predictive factors, i.e. those that are socioeconomically graded, as being potentially important targets for further investigation.

4.2 Literature review

Thirty eight studies[1;80;81;114;119-151;184] have examined the association between at least one indicator of SEP in adulthood and hysterectomy (for summarised details of studies see appendix 2). Most of these studies[80;81;114;119-123;125-129;132-134;136;137;139;140;142;144;146;150] provide evidence to suggest that the association between SEP in adulthood and hysterectomy is inverse, with women of lower SEP experiencing higher risk of hysterectomy. While the number of studies already published may lead to questions about the need for further research of the association between SEP and hysterectomy, many of the studies have limitations and the relationship is not consistent across all studies, with some studies finding a positive association[130;141;145;151] and the majority of studies which included British women finding no overall association.[1;131;149] Further, despite the attention which the association between adult SEP and hysterectomy has received the independence from each other of different indicators of SEP has rarely been examined, a life course perspective has only been employed twice, little attempt has been made to explain the associations found and the potential complexity of the associations have been overlooked. This complexity is demonstrated by the fact that in a number of studies which found no overall association there was evidence of associations which were age-,[150] reason for hysterectomy-[1;150] or SEP indicator-[122;123;131;135;137-139] specific.

4.2.1 SEP in early life

A major limitation of the existing work on the association between SEP and hysterectomy is that only two studies[80;139] have examined the association between SEP in early life and hysterectomy risk. This is despite the fact that there is a large amount of evidence to suggest that SEP in early life influences a myriad of adult health outcomes and that this cannot be fully explained by the correlation between SEP in childhood and adulthood.[188-192] The benefits of studying SEP in early life and its association with adult health include the: insight it provides into the stages of life during which adult disease risk is affected; clues about the pathways on which SEP across life may act to influence adult disease risk; and an improved understanding of inequalities in adult health outcomes.

In analyses using data from the NSHD with follow-up to age 52 years, father's occupational class was inversely associated with hysterectomy.[80] In the only other study,[139] conducted in the USA, there was no significant association between hysterectomy and parental education level, income or occupation at the time of the study participant's graduation from high school. While both studies used appropriate longitudinal designs, in the American study, parent's education was retrospectively reported by study members and time of high school graduation may not be the period in earlier life when SEP is influential.

Childhood SEP could influence hysterectomy risk not only through its association with SEP in later life but also because it is associated with a range of factors which influence hysterectomy risk including gynaecological development, initiation of behaviours (such as sexual intercourse), timing of first childbirth and development of attitudes and approaches to medical care.

Further studies are needed to assess whether SEP in early life does influence hysterectomy risk in different populations and across different time periods and to identify which indicators of early life SEP are most important given only father's occupational class has been considered in the NSHD to date. Given the correlation between childhood SEP, education and SEP in adulthood it is also important to consider whether any effect of childhood SEP is independent of SEP in later life.

4.2.2 Education

The association between education and hysterectomy has been studied frequently.[80;81;114;119-144] All but four studies[124;130;141;143] have found that women with lower levels of education had a higher risk of hysterectomy. Two[130;141] of the studies which found no effect were conducted amongst minority groups in the USA who had much lower overall levels of education and faced greater challenges to accessing medical care than the majority of people. While such studies are important they are not generalisable. The third study to find no effect[143] is also not generalisable as only female military veterans were examined. The fourth study[124] grouped education into only two categories whereby analyses may not have been sufficiently sensitive to detect any effects which existed.

Some study findings[133;137;138] suggest that the relationship between education and hysterectomy may not be linear with women who have a limited amount of education experiencing higher risk of hysterectomy than women with less or more education. Further, there is evidence in some populations that the association may attenuate with age[80;81] and that it may vary by reason for hysterectomy.[137]

That the association between education and hysterectomy is generally consistent across time and place, despite the use of different study designs and different levels of adjustment for confounders, implies that education is an important predictor of hysterectomy.

Bombardier and colleagues,[193] have suggested that higher levels of education could be associated with lower surgery rates because: of an association between higher education and better health status; a greater confidence of doctors in more highly educated patients to comply with non-surgical alternatives and be considered to have sufficient living conditions for outpatient treatment; more highly educated people valuing their time and having more responsibility whereby they are less willing and/or able to give up time for surgery and recuperation. The last of these potential explanations was also proposed by authors of a study of the treatment preferences of women with heavy menstrual bleeding,[194] which found that women of low education were more likely to state a preference for hysterectomy than women with higher levels of education. Also proposed as an explanation of this finding, was a difference in the amount and timing of information on new medical technologies which women of different levels of education receive. A further potential explanation of the association between education and hysterectomy is provided by van der Meer and Mackenbach[185] who found that lower educational level was associated with higher general practice consultation rates after controlling for health status and health insurance.

While education could be influencing hysterectomy risk by influencing factors which influence medical need or supply and demand factors, alternatively, it could be that an association exists only because of education's association with other indicators of SEP, which themselves are more closely associated with hysterectomy risk. This is possible given education reflects childhood SEP and determines indicators of adult SEP such as occupation and income.[183]

4.2.3 Occupational class

The association between occupational class, measured either at the individual (i.e. own) or household (i.e. spouse or head of household) level, and hysterectomy has also been widely studied.[1;80;81;114;119;123;131;133;135;136;138;139;147-149] The evidence for an association between occupational class and hysterectomy is less consistent than for education, and in some studies differs dependent on whose occupational class is considered.

The earliest study[147] to examine hysterectomy by occupation was greatly limited due to its unconventional categorisation of occupation. Studies which have considered occupational class using more conventional occupation classification scales have found either some evidence of an inverse association[1;80;81;114;119;133;135;136;138;139] or no association with hysterectomy.[123;131;149]

Of those studies which found an inverse association between occupational class and hysterectomy this was not always consistent if individual and household levels of occupational class were both tested. In all three analyses of the NSHD,[80;81;133] partner's occupational class was inversely associated with hysterectomy, attenuating with age, whereas own occupational class was not. Conversely in an American study,[139] own occupational class was a better predictor of hysterectomy risk than partner's occupational class although this difference between studies may be due to differences in access to medical care between countries.

The relationship between occupational class and hysterectomy has been found to vary by reason. Vessey and colleagues[1] concluded that occupational class was not a major determinant of hysterectomy overall. However, they found that women from lower occupational classes experienced higher rates of hysterectomy for menstrual problems and 'other' reasons but lower rates for fibroids and endometriosis than women from higher occupational classes highlighting the need to consider variations in association by reason for hysterectomy.

As mentioned previously, education and adult occupational class are correlated - educational level influences future occupation[183] - however, few authors have considered whether both indicators are acting on the same or different pathways to influence hysterectomy risk, or whether one of the indicators is associated with hysterectomy only because it is correlated with the other. Dharmalingam and colleagues[119] considered this to an extent in their analyses. Both education and occupational class were associated with hysterectomy in unadjusted analyses and, education remained significantly inversely associated after adjustment for occupational class leading the authors to conclude that the two factors play complementary roles rather than being part of exactly the same underlying factor. However, they did not report the result of adjusting the association between occupational class and hysterectomy for education. The independence of education from occupational class has also been demonstrated in another study[136] although in a further study occupational class explained the association between education and hysterectomy.[139] This requires further investigation.

4.2.4 Income

The other major indicator of SEP examined in relation to hysterectomy is income.[121;122;124;129;135;138;139;145;146] Some studies have found positive associations between income and hysterectomy,[135;138;145] others inverse associations[121;122;129;146] and two found no association.[124;139] Of those studies which found a positive association, two[135;138] had found inverse associations between hysterectomy and both occupational class and education. This suggests that the pathways on which income operates to influence hysterectomy risk may be different to those on which other important indicators of SEP act perhaps because income is linked more directly to ability to access health services than other indicators of SEP, especially in countries with private health care.

In four of the studies,[135;138;145;146] three being those which found a positive association, a linkage design was used. This design has more limitations than other designs as the denominators used in analyses were estimated using routinely collected data and may incorrectly include women who have previously had a hysterectomy. While information on individual level income was linked to women who had a hysterectomy using census data in two studies[135;138] in the other two[145;146] income was assigned based on the average income within the postcode of residence which may not accurately reflect the true income of the women or their households. In addition, in all these linkage studies, because of the limited amount of additional information which could be linked to the women, the possibility that the results were explained by confounding cannot be ruled out.

While the inconsistencies in findings between different studies of the association between income and hysterectomy could be partially explained by differences in study designs, it is unlikely to provide a full explanation. Another possible reason is the relative instability of income – income fluctuates more, over time and between places, than other indicators of SEP whereby the point at which income is measured in relation to timing of hysterectomy, the birth cohorts studied and country of study is more important than in studies of other indicators of SEP.

4.2.5 Other indicators of SEP

A number of other indicators of SEP in adulthood have been examined in relation to hysterectomy risk. These include poverty levels,[137;141] health insurance ownership,[151] home ownership,[139] employment status[144] and area-based SEP.[150]

The results from the studies of poverty are not particularly useful. In one study[137] which found no independent association between poverty and hysterectomy, poverty was measured as residence in a poverty census enumeration district which may not accurately reflect individual level exposure even though this would be expected to more closely predict hysterectomy risk than neighbourhood level exposure. The other study[141] had a non-representative study population and so although this study found that less poverty was associated with increased risk of hysterectomy this is not generalisable to populations with less restrictions in access to health care than faced by the Mexican-American women living in the southwest USA who were included in the study population.

Ownership of health insurance was found to increase likelihood of hysterectomy in an Irish population[151] which suggests that like income, ownership of health insurance influences access to medical care more directly than other indicators of SEP.

Home ownership was not associated with hysterectomy risk in the only study[139] which has considered this. Women who were in full-time employment had lower odds of hysterectomy than women who were sick or unemployed.[144]

In a study[150] of area-based SEP an inverse association with hysterectomy was found. This was a linkage study which assigned exposure status at the group level and so faces limitations if it is considered as a proxy of individual level SEP, however, it does suggest that there may be contextual influences also acting to determine hysterectomy risk.

4.2.6 General appraisal of published studies

4.2.6.1 Study designs

Linkage, cross-sectional and cohort designs have been used to examine the association between SEP and hysterectomy. The limitations of linkage studies have been discussed above.

Both cross-sectional and cohort designs are appropriate especially for examination of educational level which is usually fixed by early adulthood and accurately reported across adult life. However, cross-sectional designs are more limited in studies of other indicators of SEP as exposure status is measured after the outcome has occurred. Even where reverse causality is unlikely this is problematical as most indicators of an individual's SEP vary over time and so could change between hysterectomy and measurement whereby SEP at the most influential time point may not have been recorded.

4.2.6.2 Countries of study

Studies have been conducted in a range of countries, the majority in the USA[120-122;125;129;130;137;139;141-143;145;147] but also in the UK,[1;80;81;131;133;149] Australia,[114;124;127;128;132;134] Finland,[123;135;138] Italy,[126;150]Denmark,[136] Switzerland,[148] New Zealand,[119] Ireland,[151] Sweden[144] and the Netherlands.[140;146] There are differences in health care organisation, most importantly in levels of privatisation of medical care, between these countries. However, while there is considerable variation in hysterectomy rates,[104] socioeconomic gradients are quite consistent across countries. This suggests that differences in health care organisation, most importantly the levels of privatisation of medical care, may account for variation in hysterectomy rates but they are not a major explanation of socioeconomic gradients.

4.2.6.3 Definition of hysterectomy

In the majority of studies hysterectomies for any reason were included. In the three studies[1;136;150] which did analyse associations by reason for hysterectomy some variation in findings by reason were identified.

4.2.6.4 Measurement of SEP

The majority of studies measured SEP at only one time point and considered only one or two indicators (see appendix 2). While informative when developing a framework of indicators of SEP which influence hysterectomy risk, measurement of SEP in this way is unlikely to capture fully lifetime socioeconomic circumstances.

4.2.6.5 Age range of study populations

Socioeconomic differentials in health outcomes are dynamic and can change over time.[188] If the age range of a study population is wide, cohort-specific effects may go undetected. By grouping together women born in different decades who will have experienced different sets of social circumstances, relative and absolute levels of adversity and societal pressures and expectations results may tend towards the null. Despite this a number of studies, as shown in appendix 2, have used study populations including a wide range of birth cohorts.

4.2.7 Summary of findings from the literature review

Evidence from studies to date suggests that education is the most consistent predictor of hysterectomy with adult occupational class usually found to be associated in the same inverse direction. Results for income are much less consistent. As only two studies have examined the influence of early life SEP whether there is any effect of SEP in earlier life on hysterectomy risk is difficult to assess. While existing studies have identified that socioeconomic variations in hysterectomy exist they have a number of limitations and further work is justified.

An important limitation of existing work is that despite the correlation between indicators of early life SEP, education and adult SEP there is no clear understanding of whether these different indicators are acting independently of each other or not. If this was understood it may aid identification of those pathways most likely to be operating between SEP and hysterectomy.

There has also been no attention given to the potentially dynamic nature of the association between SEP and hysterectomy over time despite the fact that associations found may vary by birth cohort as trends in hysterectomy and socioeconomic conditions, especially for women, have changed over time.

4.2.8 Previous work using data from the NSHD

SEP is the only predictor of hysterectomy to have been explicitly investigated in the NSHD to date. Three papers which examined the association between SEP and hysterectomy in the NSHD have been published all of which are discussed in the appropriate sections above.[80;81;133] In summary, this previous work has examined the association between educational attainment, own and partner's occupational class and hysterectomy with follow-up to ages 43[133] and 52 years.[80;81] The association between father's occupational class in childhood and hysterectomy up to age 52 years has also been briefly investigated.[80] The main findings from these analyses were, as in a number of other studies, that partner's occupational class and education were inversely associated with hysterectomy. The effect of education appeared to be non-linear - women with minimal rather than no qualifications had the highest rates of hysterectomy compared to women with a degree or higher. Further, this association attenuated with age. Father's occupational class was also inversely associated with hysterectomy rates and this association did not attenuate with age.

These analyses can be updated, with follow-up to age 57 years now possible. This will be informative given the attenuation of the size of some associations with age. Further, in previous analyses all hysterectomies have been grouped together. More information about the associations found and the pathways that may underlie them could be discovered by examining the associations by reason and by examining a wider range of indicators of SEP from across life.

All women in the NSHD were born in the same week of the same year and so in order to test whether the association between SEP and hysterectomy is stable across birth cohorts comparisons will be made to other cohorts of British women born in different decades of the twentieth century.

4.3 Specific objectives of the chapter

The specific objectives to be addressed in this chapter are:

i. to examine whether a range of indicators of SEP from time points across life are associated with hysterectomy rates in the NSHD
ii. to examine whether the associations between hysterectomy and indicators of SEP at the same time period in life and, at different stages of life are independent of each other
iii. to examine whether the associations between indicators of SEP and hysterectomy rates differ by reason for hysterectomy
iv. to make comparisons of the associations between indicators of SEP and hysterectomy in the NSHD with the associations in two other British cohorts

4.4 Methods

4.4.1 Study populations

In addition to the NSHD, details on which were provided in chapters 2 and 3, and which is the study population used to examine objectives (i) to (iii), data from the British Women's Heart and Health Study (BWHHS) and the Aberdeen 'Children of the 1950s' Study were used to address objective (iv). These British cohorts are useful for comparison with the NSHD as they include women born in the decades either side of 1946.

The BWHHS is a cohort study of 4,286 women, born between 1919 and 1940, randomly selected from general practitioner lists in 23 British towns. Baseline data were collected between 1999 and 2001, when study members were aged 60 to 79 years, at which time gynaecological history and details of childhood socioeconomic circumstances were obtained retrospectively and details of contemporary socioeconomic circumstances were recorded.[68;195]

The Aberdeen 'Children of the 1950s' study is a cohort of 12,150 men and women born in Aberdeen between January 1950 and December 1955 who attended Aberdeen primary schools, participated in surveys in 1962, of whom 99% were successfully traced (N = 12,115) in 1999.[196] As of October 2003, 291 of those traced had emigrated outside the UK, 62 were in the armed forces or institutionalised and 479 had died. The remaining 11,282 (5,540 women) were mailed a follow-up health questionnaire to which 3,751 (67.7%) of the females responded. This postal questionnaire sent in 2000/1, when study members were aged 45 to 51 years, collected information on a range of information including SEP and hysterectomy.

4.4.2 Main outcome variable

Hysterectomy with or without oophorectomy. In the two cohorts used for comparison the same definition of hysterectomy was used and is as reported at the baseline assessment in the BWHHS and as reported in the 2000/1 questionnaire in the Aberdeen cohort.

4.4.3 Main explanatory variables

Indicators of SEP from across life. Those used to address objectives (i) to (iii) were:
- in childhood: father's occupational class; father's and mother's educational levels; family housing tenure; crowding; sharing a bedroom; access to an indoor bathroom; access to running hot water
- educational level attained
- in adulthood: own occupational class; head of household occupational class; housing tenure; income

All variables above except parental educational levels and income were also used to address objective (iv), in addition age at leaving education was included in this final set of analyses.

4.4.4 Ascertainment of indicators of SEP

The indicators of SEP used to address objectives (i) to (iii) were selected a priori to represent a wider range of indicators of SEP from across life than have been tested in any study previously.

Maternal and paternal educational levels were ascertained during interviews in childhood and were categorised, as in other analyses of the NSHD[197] to take account of the fact that some parents did not attend secondary school but pursued further education (FE) later in life and, that not all FE led to the attainment of formal qualifications. These variables were grouped into four categories: secondary and FE or higher; secondary only or, primary and FE or higher; primary and FE (no qualifications attained); primary education only. All other indicators of childhood SEP in the NSHD were ascertained during the data collection at age 11 years through responses to a range of questions about socioeconomic conditions at that time (information was taken from data collections at ages 15, 4 or 8 years if missing at age 11, the number of women for whom information had to be taken from other years varied by variable but applied to up to only 8 women except for father's occupational class where it applied to 77). Father's occupational class was classified according to the Registrar General's social classification and for objectives (i) to (iii) categorised into 4 groups: I or II (Professional or Managerial/Technical); III Non-manual (Skilled); III Manual (Skilled); IV or V (Partly skilled or Unskilled). Level of crowding was determined by calculating the number of persons per room and categorised into 3 groups: ≤ 1; 1.1 – 1.9; ≥ 2. Family housing tenure was considered as a binary variable: owner-occupied vs. not owner-occupied. Sharing a bedroom, access to an indoor bathroom and access to running hot water were also coded as binary variables (yes vs. no).

Education level was ascertained at age 26 years and was grouped into five categories: degree or higher; advanced secondary qualifications ('A' levels or equivalent); ordinary secondary qualifications ('O' levels or equivalent); below secondary qualifications; no qualifications.

All measures of adult SEP except income were ascertained during the home visit at age 43 years (with information recorded at age 53, 36 or 26 years used if missing at age 43, this varied by variable and applied to between 93 and 281 women). Both adult occupational class measures were classified and categorised in the same way as father's occupational class, described above. As for the equivalent measure from childhood, housing tenure was considered as a binary variable. Income was ascertained during the home visit at age 36 years at which time women were asked what their average take-home pay per week was. This was grouped into three categories: ≥£100; £40 - £99; < £40 per week.

These same indicators of SEP were used to address objective (iv) as all were available in at least one of the other two cohorts, except parental educational levels and income which were either not available or not measured at an appropriate age in the other two cohorts. An additional education variable, age at leaving school was included in these analyses as there was no measure of educational level attained in the BWHHS and it was considered important to have a measure of education for all three cohorts. Whether cohort members were still in education after reaching minimum legal school leaving age or not was ascertained from prospective data collection across adolescence and early adulthood in the NSHD. This was considered as a binary variable: still in education after minimum school leaving age vs. not.

All measures of childhood SEP in the BWHHS were retrospectively recalled during the baseline data collection. In the Aberdeen cohort, father's occupational class was recorded at birth and all other measures were collected retrospectively in the 2000/1 questionnaire by asking about conditions at age 12 years. All measures of adult SEP and education were measured at the time of the baseline data collection and 2000/1 postal questionnaire respectively.

4.4.5 Relative indices of inequality

Relative indices of inequality (RII) were used to address objective (iv) as they enabled direct comparison of SEP variables between cohorts - they take account of the differences between cohorts in the proportions of women in the different categories of a socioeconomic variable.[198] For each indicator of SEP a score between 0 (highest SEP) and 1 (lowest SEP) was assigned to each category based on the proportion of the population above the mid-point in that category. For example, if 10% of the population were in social class I women in this group were represented by the range 0 to 0.1 and thus were allocated the score 0.05 (0.1/2). If 20% of the population were in the next highest group, social class II, then this social class was allocated a score 0.20 (0.1 + 0.2/2) and so on. The RII was then obtained by regressing the outcome on each of these SEP scores using Cox's proportional hazards models and was directly interpretable for each indicator of SEP used as comparing women of the lowest SEP (1) with the highest SEP (0). To calculate these scores the same categorisations of indicator were used as for objectives (i) to (iii) with the exception of the three occupational class measures where 6 categories (I, II, IIINM, IIIM, IV and V) were used.

4.4.6 Analyses

4.4.6.1 Analyses to address objective (i) - unadjusted associations

Cox's proportional hazards models were used to test the unadjusted association between each indicator of SEP and hysterectomy.

4.4.6.2 Analyses to address objective (ii) – adjusted associations

The association between each indicator of SEP and every other was individually tested using chi-squared tests.

Indicators of SEP which were not associated with hysterectomy rates in unadjusted models were not included in multivariable models. This was to avoid testing associations which were unlikely to produce significant results other than by chance and to limit the overall number of statistical tests performed.

In a first set of analyses, the independence from each other of the indicators of childhood SEP which were significantly associated with hysterectomy in unadjusted analyses was tested. This was done by considering indicators in pairs, adjusting both variables for each other in a survival model and using likelihood ratio tests to compare models with only one of the variables included to a model in which both variables were included. In a second set of analyses, the same strategy was used to examine the independence from each other of the indicators of adulthood SEP which were significantly associated with hysterectomy in unadjusted analyses.

Once the indicators of SEP from childhood which acted independently of each other had been identified these were adjusted for education and indicators of SEP in adulthood to test the independence of childhood SEP from SEP in later life.

The independence of education from indicators of SEP in childhood and adulthood was examined by pairing an indicator of SEP from childhood and an indicator of SEP in adulthood with education, adjusting education and the other variable for each other and then using likelihood ratio tests to compare models with only one of the variables included with a model in which both variables were included. In a final model, mutual adjustment for education, an indicator of SEP in childhood and an indicator of SEP in adulthood was performed.

In addressing this objective it was ensured that all models compared were nested within each other and were based on the same N.

4.4.6.3 Analyses to address objective (iii) – reason for hysterectomy

Using the competing risks framework described in chapter 3 the association between each indicator of SEP and subsequent hysterectomy rates by reason for hysterectomy was assessed.

4.4.6.4 Analyses to address objective (iv) – cross-cohort comparisons

The work to address this objective was carried out in collaboration with Dr Debbie Lawlor of the Department of Social Medicine, University of Bristol who performed all analyses on the BWHHS and Aberdeen cohorts.

Unlike in the analyses to address objectives (i) to (iii), follow-up in this set of analyses was in years since birth to ensure comparability between cohorts. The follow-up times of women who had not had a hysterectomy were censored at the age of completing the baseline questionnaire in the BWHHS and at age of completing the 2000/1 questionnaire in the Aberdeen study.

To ensure comparability between results for different indicators of SEP only women who had complete data on hysterectomy and all indicators of SEP (BWHHS N=3,208; NSHD N=1,394; Aberdeen N=3,208) were included in the analyses to address this objective.

Rates of hysterectomy in five-year age-bands were calculated for each cohort. Cox's proportional hazards models were then used to test the unadjusted association between each indicator of SEP and hysterectomy in each cohort with indicators of SEP entered into models as continuous index of inequality scores.

4.5 Results

4.5.1 Results from analyses to address objective (i) - unadjusted associations

Of the indicators of childhood SEP examined, father's occupational class, maternal education and housing were found to significantly predict hysterectomy rates in unadjusted survival analyses. There were no significant associations between other indicators of childhood SEP and hysterectomy, table 4.1. All three indicators were inversely associated with hysterectomy rates whereby, women whose fathers were of lower occupational class, whose mothers had lower educational levels and who did not live in owner-occupied housing had higher rates of hysterectomy than women whose fathers had higher occupational class, whose mothers had high educational levels and who lived in owner-occupied housing (as shown in figure 4.1 for father's occupational class). Women whose mothers were educated only to primary level had rates of hysterectomy 86% higher than women whose mothers had been educated to greater than secondary level. Tests for trend across categories of father's occupational class and maternal education were also significant.

In a survival model with complete follow-up i.e. from age at menarche to age 57 years, there was significant interaction between educational level and time (p=0.006) which is evidence that the proportional hazards assumption was violated. Examination of the Kaplan-Meier survival plot, see figure 4.2, suggested that this was due to an attenuation in the size of the association between education and hysterectomy over time - from approximately 35 years after menarche onwards the plotted lines were no longer diverging and were instead running parallel to each other. This attenuation was identified in earlier work on the NSHD with follow-up to age 52 years.[80;81] As in the previously published analyses this violation of the proportional hazards assumption was overcome by using piecewise models in which the follow-up time was split in two and separate models covering the different follow-up periods were used. The appropriate place to split follow-up time was identified as age 44 years and when this was done there was no significant interaction between education and time in the model with follow-up from age at menarche to age 44 years or in the model with follow-up from age 44 to 57 years. Educational level was strongly associated with hysterectomies performed up to age 44 years, table 4.2 – women with below secondary education qualifications had rates of hysterectomy in earlier adulthood just under 8 times higher than women who had a degree or higher. This association was not linear as women who had some but below secondary qualifications had higher rates of hysterectomy than any other group of women including those with no qualifications. There was no significant association between education and hysterectomies performed above age 44 years. Despite this attenuation, at all ages women with a degree or higher had lower cumulative rates of hysterectomy than women with fewer or no qualifications.

A similar attenuation in the size of association over time was found when examining adult head of household occupational class. Due to the interaction between adult head of household occupational class and time, two piecewise models one with follow-up from age at menarche to age 44 years and one with follow-up from age 44 to 57 years were again used. Adult head of household occupational class, like educational level, was inversely associated with hysterectomy rates up to age 44 years but not with hysterectomy rates between 44 and 57 years, table 4.2. There were no significant interactions between own occupational class, adult housing or income and time and so full follow-up time was used to model the association between these indicators of SEP in adulthood and hysterectomy. Adult housing did not predict hysterectomy rates but own occupational class and income were inversely associated with hysterectomy rates – women in occupational class IV or V had rates of hysterectomy 36% higher than women in class I or II and women with a weekly income of <£40 had rates of hysterectomy 60% higher than women with a weekly income of ≥£100, table 4.2.

4.5.2 Results from analyses to address objective (ii) – adjusted associations

Each indicator of SEP was significantly associated with all others in expected directions (results not shown). Women whose childhood SEP was low, as indicated by any measure considered, were less likely to have attained a high educational level and more likely to have lower adult SEP than women whose childhood SEP was high.

In analyses testing the independence of indicators of childhood SEP from each other it was found that the effect of childhood housing was explained by father's occupational class. When these two indicators were adjusted for each other the association between father's occupational class and hysterectomy remained significant whereas the association between childhood housing and hysterectomy attenuated and was no longer significant. When father's occupational class and maternal education were adjusted for each other, the effect of both indicators attenuated slightly and while the overall effects of both variables did not retain statistical significance as indicated by p-values from likelihood ratio tests, there were still significant differences in hysterectomy rates between different categories of each variable as signified by the fact that some 95% confidence intervals did not include 1, table 4.3.

In analyses testing the independence of indicators of adulthood SEP from each other, run as piecewise models to allow for the interaction between head of household occupational class and time, it was found that the effect of own occupational class was not independent of head of household occupational class up to age 44 years, with results from likelihood ratio tests suggesting that if head of household occupational class was known there was no benefit in also including own occupational class in the model (results not shown). In models with follow-up from age 44 to 57 years neither indicator predicted hysterectomy. In both periods of follow-up results from likelihood ratio tests comparing models with both income and head of household occupation included to models with each variable entered individually suggested, as demonstrated by non-significant p-values, that there was no benefit in including both variables in the same model as they predicted hysterectomy rates in the same way.

When adjusted for education and adult head of household occupational class, taking into account the time varying effect of these two variables, the size of the associations between father's occupational class, maternal education and hysterectomy attenuated, this appeared to be due to the effect of adjusting for education rather than adjusting for adult head of household occupational class, table 4.4.

In a final model, with follow-up only to age 44 years, given there was no clear evidence of an effect of SEP on hysterectomy rates performed at later ages, when maternal education, educational attainment and adult head of household occupational class were all adjusted for each other, education was the only indicator of SEP which had a significant effect on hysterectomy rates which was independent of the other indicators of SEP, table 4.5. This effect was large with women who had lower than secondary level qualifications experiencing rates of hysterectomy over 10 times higher than women who had a degree or higher up to age 44 years. Although not significant after adjustments the point estimates of effect for maternal education remained close to 2.

4.5.3 Results from analyses to address objective (iii) - reason for hysterectomy

For some indicators of SEP in childhood there was no clear evidence of variation in effect on hysterectomy rates by reason – the associations between father's occupational class, maternal education, housing and sharing a bedroom and hysterectomies for each different reason were all in the same inverse direction (see appendix 3). However, for other indicators of SEP in childhood there was some evidence that their effect on hysterectomy did vary by reason. Women who in childhood lived in more crowded conditions, who did not have an indoor bathroom and who did not have running hot water had lower rates of hysterectomy for fibroids and prolapse but had higher rates of hysterectomy for menstrual disorders, cancer and other reasons compared to women who had higher SEP as indicated by these variables, table 4.6. Further, grouping all hysterectomies together was masking an inverse association between paternal education and hysterectomies for cancer and menstrual disorders.

While there was no clear evidence of a difference in the association between education and hysterectomy by reason in models with follow-up to age 44 years, in models with follow-up from age 44 to 57 years, education was inversely associated with hysterectomies for menstrual disorders but positively associated with hysterectomies for fibroids, table 4.7. In both periods of follow-up adult head of household occupational class was positively associated with hysterectomies for fibroids with women of lower occupational class experiencing lower rates of hysterectomy for this reason compared to women of higher occupational class. Conversely, mirroring the overall association found, adult head of household occupational class was inversely associated with hysterectomies for menstrual disorders and cancer, table 4.8. There was no clear pattern of variation in association by reason for hysterectomy when considering own occupational class or income. Women who did not live in owner-occupied housing had lower rates of hysterectomy for fibroids, menstrual disorders and prolapse and higher rates of hysterectomy for cancer and other reasons compared to women who were living in owner-occupied housing.

The most consistent association between SEP and hysterectomy was seen when examining hysterectomies for cancer. All indicators of SEP were inversely associated with hysterectomies for cancer, with women of lower SEP experiencing higher rates of hysterectomy for cancer than women of higher SEP. An inverse association was also consistently found when considering hysterectomies for menstrual disorders. Although not found for all indicators of SEP, there was also some evidence that the association between SEP and hysterectomy may be acting in the opposite direction on hysterectomies for fibroids and prolapse.

4.5.4 Results from analyses to address objective (iv) - cross-cohort comparisons

In unadjusted analyses, table 4.9, women in the BWHHS (the oldest cohort) who had an adverse SEP in childhood had lower hysterectomy rates than women who had a better position. For example, women whose fathers were in the lowest occupational class had rates of hysterectomy 27% lower than women whose fathers had the highest occupational class. This is the converse of what was found in the NSHD and also the Aberdeen cohort where adverse SEP in childhood was associated with higher hysterectomy rates. In the Aberdeen cohort women whose fathers were in the lowest occupational class had rates of hysterectomy over twice as high as women whose fathers were in the highest occupational class. Similarly, lower educational level was associated with reduced rates of hysterectomy in the BWHHS whereas in the NSHD up to age 44 years and in the Aberdeen cohort across the full length of follow-up (i.e. up to age 51 years), lower educational status was associated with increased rates of hysterectomy.

Unlike the findings in the NSHD neither own or head of household occupational class were associated with hysterectomy in the BWHHS or Aberdeen cohorts.

The relationships between childhood indicators of SEP and hysterectomy in the BWHHS and Aberdeen cohorts were independent of adult SEP (results not shown). For more details and results from these comparative analyses see appendix 4.

4.6 Discussion

4.6.1 Main findings

Indicators of SEP at different time points across life were inversely associated with hysterectomy rates in the NSHD. However, the associations between father's occupational class, maternal education, adult head of household occupational class and hysterectomy were largely explained by educational level. The associations between education, adult head of household occupational class and hysterectomy were non-linear and attenuated with age and whereas women who had no educational qualifications had rates of hysterectomy over 8 times higher than women who had a degree or higher up to age 44 years, there was no significant association between education and hysterectomy between ages 44 and 57 years.

Although not fully consistent there was some evidence that the effect of SEP on hysterectomy may vary by reason for hysterectomy. Indicators of SEP were associated with hysterectomies for cancer and menstrual disorders in the same inverse direction as found overall whereas some indicators of SEP were associated with hysterectomies for fibroids and prolapse in the opposite direction.

Similar inverse associations between SEP and hysterectomy overall to those found in the NSHD were found in a younger cohort, the Aberdeen 'Children of the 1950s' study, whereas the converse was found in an older cohort, the BWHHS, suggesting that the relationship between SEP and hysterectomy may be dynamic and have changed over time.

4.6.2 Comparison with other studies

In analyses of the effect of adult SEP on hysterectomy in three other British studies[1;131;149] no clear associations were found. These studies grouped together women born in different decades and did not consider variations in the effect of SEP by age at hysterectomy and so effects similar to those found in this study may have gone undetected. Further, two of the studies considered only occupational class which may not capture fully the aspects of SEP which are most influential, especially as the effect of occupational class in the NSHD appears to be explained by educational level.

While finding no clear associations when grouping all hysterectomies together Vessey and colleagues,[1] authors of one British study, did find evidence that the effect of SEP, as indicated by husband's occupational class, was inversely associated with hysterectomies for menstrual problems and cancer and positively associated with hysterectomies for fibroids which is similar to what was found when considering the association between SEP and reason for hysterectomy in the NSHD.

No existing British studies had examined the effect of income on hysterectomy rates. The finding of an inverse association between adult income and hysterectomy rates in the NSHD is similar to what has been found in some studies[121;122;129;146] but not others conducted in different countries.[124;135;138;139;145] That the association between income and hysterectomy is in the same direction as the associations between other indicators of SEP and hysterectomy rather than in the opposite direction is the converse of what is often found when examining socioeconomic variation in surgical utilisation.[193] This is probably because the NHS in the UK means that access to health care is not directly limited by income in the same way that it is in countries where the majority of health care is provided privately.

In the only existing studies to explicitly examine the relationship between SEP in early life and hysterectomy, detailed in the literature review, one found evidence of an inverse association[80] while the other found none.[139] The results from this latter study[139] may not be generalisable to a UK population as it was conducted in the USA where hysterectomy rates are much higher and organisation of health service provision is different.

Of the few studies which examined the inter-relationship between different indicators of SEP, two found similarly to the NSHD that education was independent of other indicators of SEP[119;136] whereas a third found that the association between education and hysterectomy was explained by occupational class.[139]

These analyses add to the previous work examining the association between SEP and hysterectomy in the NSHD[80;81;133] by assessing the effect of a wider range of indicators of SEP, testing the independence of these indicators from each other, examining the associations by reason for hysterectomy and comparing the associations to those found in two other British cohorts.

In previous analyses of the NSHD, in which women were followed-up to age 52 years there was evidence of an attenuation in the association between adult SEP and hysterectomy with age. The analyses in this chapter confirm this but suggest that there is no further attenuation between ages 52 and 57 years.

4.6.3 Explanation of findings

4.6.3.1 Why was there an association between SEP and hysterectomy?

In the NSHD, the majority of variation in hysterectomy rates by SEP in childhood and adulthood can be explained by educational level. Education, of all the indicators of SEP considered, is the strongest and only indicator of SEP which has an association with hysterectomy rates independent of other indicators of SEP. It is plausible that childhood and adulthood SEP are found to influence hysterectomy through their association with education - because of the temporal relationship between the different indicators, the association between childhood SEP and hysterectomy could have been either mediated or confounded by education and the association between adult SEP and hysterectomy was confounded by education. Indicators of childhood SEP such as father's occupation and parental education level predict educational attainment and educational attainment itself predicts indicators of adult SEP including occupation and income.[183]

There are a number of reasons which could explain why education was the strongest predictor of hysterectomy of all indicators of SEP examined. Firstly, it is possible that there are aspects of education unique to this indicator of SEP and these unique aspects are responsible for influencing hysterectomy risk. Alternatively, it could be that education, given it is predicted by early life SEP and predicts later life SEP, captures more appropriately and completely the aspects of lifetime SEP of individuals relevant to hysterectomy risk than any other one variable by itself.

Education influences a range of factors which could influence supply and demand factors or medical need for hysterectomy, these include: health behaviours; patterns of childbearing; level of knowledge about alternative treatments to hysterectomy; medical consultation rates; preferred form of treatment; ability to exercise the right to choose/suggest own preferred medical treatment (i.e. empowerment and level of autonomy); and likelihood of doctor suggesting a hysterectomy, considering/asking for patient's opinion and accepting patient's own preference. The fact that the majority of factors which education could act on to influence hysterectomy risk are associated with decision making pathways rather than medical need for hysterectomy and, that the effects on decision making could be direct rather than mediated on other pathways suggests that the influence of education on decision making and supply and demand factors is likely to be more important than the influence on medical need.

However, all indicators of SEP were inversely associated with hysterectomies for cancer, which as decisions about whether to operate for cancer are driven predominantly by medical considerations rather than supply or demand factors suggests that SEP influences the risk of medical need for hysterectomy to some extent also.

While women's and their doctor's decisions about the management of gynaecological symptoms and treatment choices may be affected directly by the woman's SEP, especially her educational level, many decisions will be influenced by other factors such as reproductive characteristics and body weight, these factors, many of which are socioeconomically graded and could mediate the associations found in this chapter, will be investigated in the following chapters.

4.6.3.2 Why does the association between SEP and hysterectomy attenuate with age?

To explain the attenuation in the association between adult SEP and hysterectomy with age found in analyses of the NSHD up to age 52 years, Marshall and colleagues[80;81] proposed that at younger ages a higher proportion of hysterectomies were performed for benign conditions such as menstrual disorders and, for these conditions, decisions about whether to undergo a hysterectomy are influenced by social factors whereas conditions for which decisions about treatment are based solely on medical considerations, such as cancer, occur in higher proportions at later ages. In addition, it was proposed that the gynaecological disorders for which hysterectomy is a treatment may have developed at later ages in women of higher SEP.

The first of these explanations presupposes that SEP acts to influence hysterectomy rates solely through its influence on decision making processes and does not take into account the possibility that SEP may actually influence the development of gynaecological disorders and therefore medical need for hysterectomy. The results of the analyses by reason for hysterectomy do not fully support this supposition as the inverse socioeconomic gradients in hysterectomies for cancer and positive socioeconomic gradients in hysterectomies for fibroids suggest that SEP is to some extent influencing hysterectomy risk through its effect on medical need. Further, there is insufficient variation in hysterectomy for cancer by age in the NSHD (see figure 2.5) to have driven the overall associations and the attenuations in these found.

Differences in the age distributions of hysterectomies for different benign reasons could however, potentially explain the attenuation in the size of association between SEP and hysterectomy. As shown in figure 2.5, up to age 44 years menstrual disorders were the most common reason for hysterectomy whereas from age 44 years onwards fibroids were. In the analyses by reason for hysterectomy, hysterectomies for menstrual disorders were inversely associated with SEP, whereas the association between some indicators of SEP and hysterectomies for fibroids was positive. This suggests that an attenuation in the size of the association between SEP and hysterectomy with age may have been seen because of a change with age in the most common benign reasons for hysterectomy which have different patterns of association with SEP.

The possibility that women with different levels of SEP developed gynaecological disorders at different ages with women of higher SEP developing conditions later cannot be tested using the data available. However, this is plausible as many factors which influence timing of the development of gynaecological disorders such as timing of childbirth and parity are socioeconomically graded. Another possible explanation is that women of higher SEP had the same risks and timing of development of gynaecological disorders as women of lower SEP but for various reasons including different patterns of childbearing and greater aversion to surgery, endured their symptoms for longer and sought and tried more alternative treatments before agreeing to a hysterectomy hence delaying their hysterectomies.

It is also possible that there was an attenuation with age because of the influence of a period effect, especially as trends in surgery can be influenced by fashion. If this was the case, in the early 1990s, at the time the attenuation began, hysterectomy for some reason would have had to become more acceptable or desirable as a treatment choice for women of higher SEP or less acceptable or desirable as a treatment choice for women of lower SEP. However, there is no evidence that this was the case although such an effect could also explain why there is no significant effect of adult SEP on hysterectomy rates in the Aberdeen cohort.

4.6.3.3 Why has the association between SEP and hysterectomy changed over time across cohorts?

The comparative analyses suggest that the relationship between early life SEP, education and hysterectomy has changed direction over time.

Social and medical changes over time are a plausible explanation of these findings. Over the course of the twentieth century there were various social and medical changes which will have impacted on the women in each of the three cohorts differentially. These include the introduction of the NHS, changes in access to medical care, attitudes and accountability of doctors, the availability of oral contraceptives, changes in completed family size and timing of childbirths, increasing levels of obesity, changes in the acceptability of some gynaecological conditions (e.g. menstrual disorders) as appropriate indications for hysterectomy and the introduction of alternatives to hysterectomy and patterns in uptake of these. Some of these factors such as patterns of childbearing are likely to have become more socially differentiated over the course of the twentieth century, while others such as access to medical care will have become less socially graded.

The paucity of information regarding trends in rates of both gynaecological disorders and hysterectomy in the UK across the twentieth century makes it difficult to establish which of the above factors play an important role in influencing differences in the relationship between SEP and hysterectomy between cohorts over time. However, it seems likely that the introduction of the NHS and the resultant changes to medical access and opinions of medical care and the changing patterns of childbearing were influential.

Another possible explanation is that methodological differences between the cohorts have caused the differences in associations found. These methodological differences are discussed in the limitations section below.

4.6.4 Limitations

One of the main limitations of the work to address objectives (i) to (iii) is that many analyses, especially those examining hysterectomy by reason, had limited power to detect effects. For example, some potentially interesting differences in association by reason for hysterectomy were found but the possibility that these differences were due to chance cannot be ruled out because the point estimates of effect were not stable and had wide confidence intervals.

While the NSHD was selected to be nationally representative at birth there has been loss to follow-up due to death, unsuccessful tracing, non-response and refusal to participate. In a comparison of the distribution of indicators of SEP between the 1,790 women included in analyses and the 757 female cohort members excluded there were significant differences in the distribution of most indicators of SEP - women not included were more likely to have been of lower SEP in childhood and adulthood than women included (results not shown). This would be expected given all reasons for loss to follow-up are predicted by SEP. This could have introduced bias although given the direction of the association found and the over-representation of women of higher SEP in the sample included in analyses, if the cohort had remained fully nationally representative the real effects may be even larger than those found.

The main limitation of the comparative work is that there are a number of methodological differences between the three study populations, an artefact of which could have been the finding of differences in results between cohorts.

The first of these differences is that women in each cohort were followed-up to different ages. However, in analyses with follow-up restricted to age 45 years in all cohorts (results not shown), the directions of association and differences between cohorts were similar to those presented. It remains possible that the association between SEP and hysterectomy could attenuate with age in Aberdeen in the future as it does in the NSHD.

SEP was measured differently in each study – prospectively in the NSHD and retrospectively in the BWHHS and the Aberdeen study (with the exception of father's occupational class in Aberdeen). However, tests of the validity of recalled childhood SEP in the Aberdeen study[199] and comparisons of self-reported data on paternal occupational class with 1931 census data in the BWHHS, suggest that there is no major bias due to retrospective self-report and that use of recalled measures leads to underestimates of real effects whereby the use of such measures is unlikely to fully explain the findings.

Markers of SEP change over time whereby indicators such as running hot water and having access to an indoor bathroom become less graded and more a marker of severe deprivation in younger compared with older cohorts. The comparative analyses by using RII accounted for this. However, using such measures in analyses assumes that the relationships between indicators of SEP and hysterectomy are linear, which was not found in analyses using standard categories of education and occupational class in the NSHD and so may not be the case in the other two cohorts either.

Only women with known hysterectomy status could be included in analyses of the NSHD and for hysterectomy status to be known women needed to have been alive and surveyed at least once since the time hysterectomy was first asked about at age 43 years. Likewise to be included in the other studies women needed to be alive and available to be surveyed during the data collections in adulthood. Therefore, only women who had survived to the age of at least 43 in the NSHD, 60 in the BWHHS and 45 years in the Aberdeen study were eligible for inclusion in the respective study populations. This may have introduced survivor bias, with greater levels expected in the BWHHS given the older age of the study population at data collection. Further differences between the three cohorts as a result of the different ages and ways in which women were recruited into the studies are also likely. While women in the NSHD and Aberdeen cohorts were recruited at birth or during childhood, women in the BWHHS were not recruited until old-age. The BWHHS is thus expected to be a more highly selected group than either of the other two study populations. This could mean that the experiences of the women in the BWHHS less accurately reflect the experiences of all women born in the 1920s and 30s, than the experiences of the women in the NSHD or Aberdeen reflect the experiences of all women born in the 1940s and 50s, respectively.

Women with missing information on hysterectomy status and with incomplete SEP data were excluded from analyses to address objective (iv). In the BWHHS and Aberdeen cohorts the women excluded due to incomplete SEP data had higher rates of hysterectomy than included women (results not shown). However, in univariable analyses including as many women as had data on the variable of interest and hysterectomy (results not shown), there was little difference in the size or direction of effects seen compared to the findings presented suggesting that the results are unlikely to be markedly influenced by selection bias due to these exclusions.

4.6.5 Strengths

This study has important strengths. In addressing objectives (i) to (iii) a wider range of indicators of SEP from across life, all of which have been collected prospectively, have been tested than in any study previously. These analyses have also taken into account the association between different indicators of SEP and identified the most important indicator of SEP in predicting hysterectomy rates. By studying these associations in detail and using survival analyses it has been possible to identify important differences by age at hysterectomy and reason for hysterectomy which may have gone undetected in other studies.

Despite some evidence of selective loss to follow-up by SEP in the NSHD, the study remains more nationally representative than many other studies.

By comparing the associations found in the NSHD with associations in two other British cohorts it has been possible to show that in addition to there being a dynamic relationship between SEP and hysterectomy across time within an individual cohort, there is also a dynamic relationship between SEP and hysterectomy across different birth cohorts.

4.6.6 Conclusions

The results to address the first three objectives of this chapter suggest that there was socioeconomic variation in hysterectomy performed at younger ages in the NSHD, more specifically that there was an association between low educational level and higher risk of hysterectomy before age 44 years and, that this was due to the influence of education on supply and demand factors and medical need.

The results from analyses comparing three cohorts are an important demonstration of the dynamic nature of the relationship between predictor variables and hysterectomy and more generally between SEP and health outcomes over time.[188] They highlight the need, when considering policy aimed at social inequalities in health and when controlling for SEP in epidemiological studies, to appreciate the possibility of marked changes in the direction and strength of effect of SEP on health outcomes over time and between places and suggest that when reporting such associations researchers should not automatically assume that results from one cohort are generalisable to cohorts from different periods or locations.

Work in the following chapters examines body weight and reproductive characteristics which could also be acting across life to influence hysterectomy risk and are some of the factors most likely to mediate or confound the association between SEP and hysterectomy.

Once these other associations have been examined and, in chapter 7 the inter-relationship between the different predictors of hysterectomy identified have been investigated it will be possible to draw further conclusions and consider the full implications of the findings.

Figure 4.1: Kaplan-Meier survival estimates for hysterectomy by father's occupational class in the NSHD (N = 1,689)

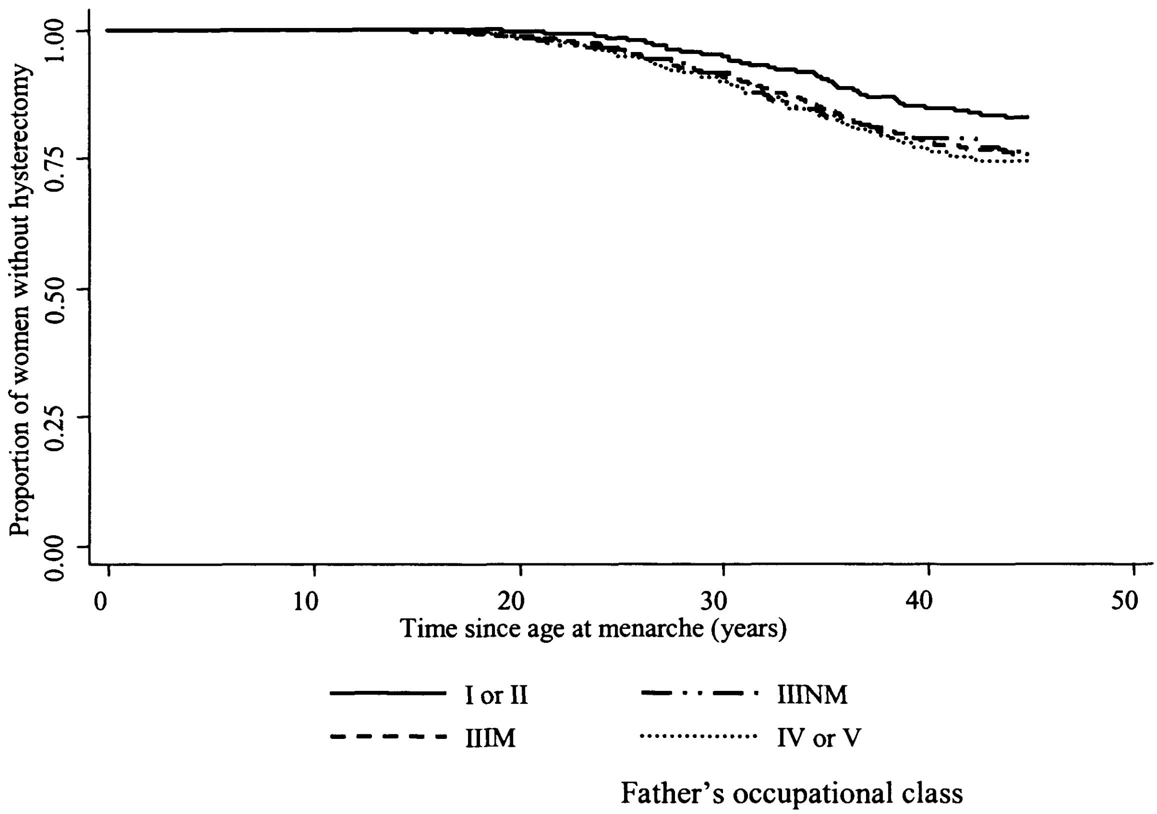
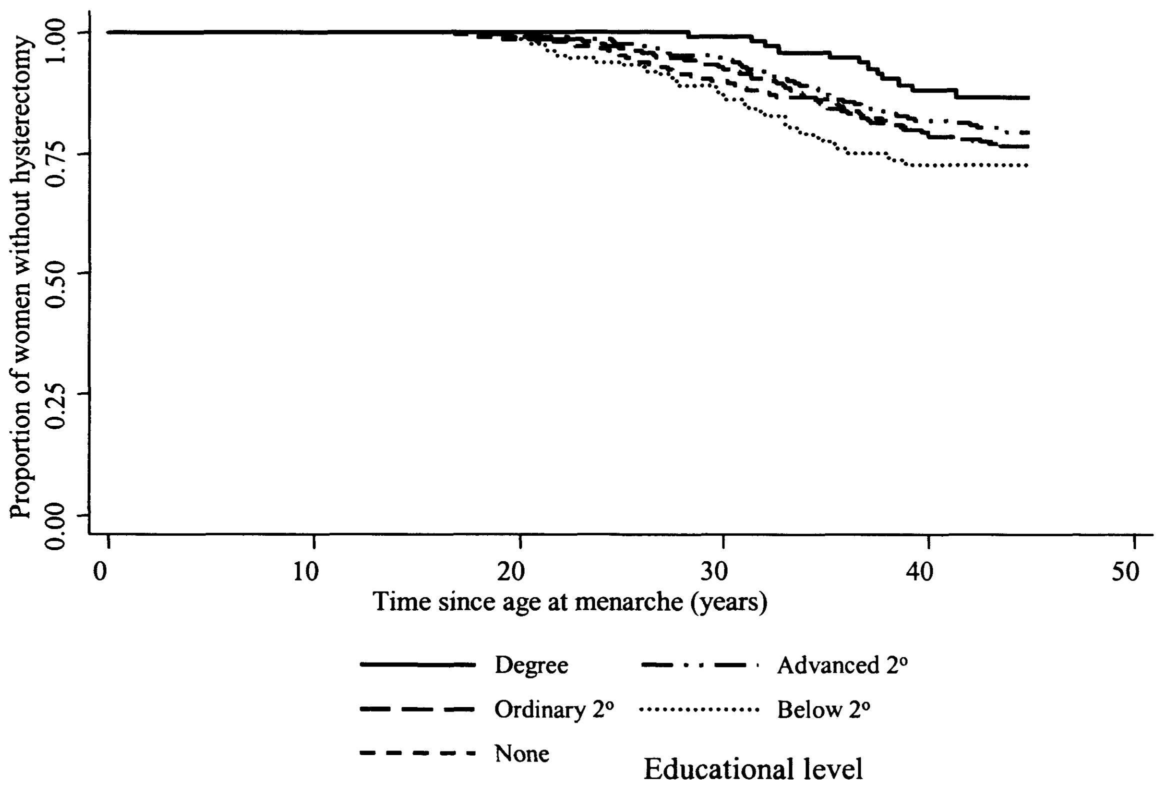


Figure 4.2: Kaplan-Meier survival estimates for hysterectomy by educational level in the NSHD (N = 1,679)



Note: 2° =Secondary

Table 4.1: Unadjusted survival analyses of the associations between indicators of SEP in childhood and hysterectomy in the NSHD

Indicator of SEP	N (%) [No. of hysterectomies]	Hysterectomy rate per 1000 women years (95% CI)	Hazard Ratio for hysterectomy (95% CI)	p-values
Father's occupational class (N=1689)				
I or II	431 (25.52) [73]	4.05 (3.22, 5.09)	1.00	0.01*
IIINM	276 (16.34) [64]	5.71 (4.47, 7.29)	1.45 (1.04, 2.03)	0.003**
IIIM	546 (32.33) [128]	5.82 (4.89, 6.92)	1.48 (1.11, 1.98)	
IV or V	436 (25.81) [107]	6.17 (5.10, 7.46)	1.59 (1.18, 2.15)	
Maternal education (N=1595)				
1 (High)	194 (12.16) [26]	3.19 (2.17, 4.68)	1.00	0.01*
2	173 (10.85) [37]	5.19 (3.76, 7.17)	1.66 (1.00, 2.74)	0.007**
3	222 (13.92) [53]	5.85 (4.47, 7.65)	1.89 (1.18, 3.02)	
4 (Low)	1006 (63.07) [230]	5.68 (4.99, 6.47)	1.86 (1.24, 2.78)	
Paternal education (N=1580)				
1 (High)	258 (16.33) [48]	4.47 (3.37, 5.94)	1.00	0.33*
2	209 (13.23) [53]	6.22 (4.75, 8.14)	1.42 (0.96, 2.10)	0.38**
3	196 (12.41) [45]	5.68 (4.24, 7.61)	1.30 (0.87, 1.96)	
4 (Low)	917 (58.04) [202]	5.46 (4.76, 6.27)	1.26 (0.92, 1.72)	
Housing (N=1763)				
Owner-occupied	609 (34.54) [121]	4.81 (4.02, 5.75)	1.00	0.04*
Not owner-occupied	1154 (65.46) [271]	5.85 (5.19, 6.58)	1.24 (1.00, 1.54)	
Crowding (persons per room) (N=1788)				
≤1	1172 (65.55) [255]	5.32 (4.70, 6.01)	1.00	0.55*
1.1 – 1.9	388 (21.70) [91]	5.87 (4.78, 7.20)	1.13 (0.89, 1.43)	0.33**
≥2	228 (12.75) [52]	5.74 (4.37, 7.53)	1.11 (0.82, 1.50)	
Shared a bedroom (N=1570)				
No	753 (47.96) [155]	5.02 (4.28, 5.87)	1.00	0.15*
Yes	817 (52.04) [189]	5.75 (4.98, 6.63)	1.17 (0.95, 1.45)	
Indoor bathroom (N=1755)				
Yes	1395 (79.49) [311]	5.49 (4.91, 6.13)	1.00	0.76*
No	360 (20.51) [82]	5.66 (4.56, 7.03)	1.04 (0.82, 1.33)	
Running hot water (N=1755)				
Yes	1359 (77.44) [294]	5.32 (4.74, 5.96)	1.00	0.15*
No	396 (22.56) [99]	6.23 (5.12, 7.59)	1.18 (0.94, 1.49)	

Parental education levels: 1 = Secondary and further or higher education ; 2 = Secondary only or Primary and further or higher education ; 3 = Primary and further education (no qualifications) ; 4 = Primary education only

* p-value from likelihood ratio test

** p-value from test for trend

Table 4.2: Unadjusted survival analyses of the associations between indicators of SEP in adulthood, education and hysterectomy in the NSHD

Indicator of SEP	N (%) [No. of hysterectomies]	Hysterectomy rate per 1000 women years (95% CI)	Hazard Ratio for hysterectomy (95% CI)		p-values
Educational level					
		Up to 44 years[a]	**Up to 44 years[a]**	**44 to 57 years[b]**	**Up to 44 years[a]**
Degree or higher	91 (5.42) [12]	0.70 (0.18, 2.81)	1.00	1.00	0.0007* 0.055♦
Advanced secondary	374 (22.28) [76]	2.59 (1.81, 3.71)	3.77 (0.90, 15.77)	1.22 (0.62, 2.42)	**44 to 57 years[b]**
Ordinary secondary	420 (25.01) [98]	3.09 (2.26, 4.21)	4.53 (1.09, 18.74)	1.42 (0.73, 2.78)	0.67* 0.68**
Below secondary	157 (9.35) [42]	5.24 (3.54, 7.75)	7.89 (1.87, 33.32)	1.28 (0.59, 2.80)	
None	637 (37.94) [142]	4.00 (3.21, 5.00)	5.95 (1.46, 24.23)	1.11 (0.57, 2.16)	
Own occupational class (N=1642)					
I & II	588 (35.81) [119]	4.93 (4.12, 5.89)	1.00		0.21*
IIINM	611 (37.21) [138]	5.55 (4.70, 6.56)	1.14 (0.89, 1.45)		0.03**
IIIM	120 (7.31) [28]	5.73 (3.95, 8.30)	1.18 (0.78, 1.77)		
IV & V	323 (19.67) [84]	6.53 (5.28, 8.09)	1.36 (1.03, 1.79)		
Occupational class of head of household					
		Up to 44 years[c]	**Up to 44 years[c]**	**44 to 57 years[d]**	**Up to 44 years[c]**
I & II	873 (49.55) [190]	2.89 (2.32, 3.61)	1.00	1.00	0.045* 0.047**
IIINM	229 (13.00) [46]	3.69 (2.51, 5.42)	1.29 (0.83, 2.01)	0.70 (0.43, 1.13)	**44 to 57 years[d]**
IIIM	454 (25.77) [114]	4.56 (3.56, 5.84)	1.62 (1.16, 2.26)	1.00 (0.72, 1.39)	0.46* 0.98**
IV & V	206 (11.69) [46]	3.30 (2.15, 5.07)	1.15 (0.71, 1.87)	1.02 (0.66, 1.57)	
Housing (N=1770)					
Owner-occupied	1438 (81.24) [325]	5.54 (4.97, 6.18)	1.00		0.98*
Not owner-occupied	332 (18.76) [71]	5.40 (4.28, 6.82)	1.00 (0.77, 1.29)		
Income (per week) (N=875)					
≥£100	134 (15.31) [23]	4.09 (2.72, 6.15)	1.00		0.10*
£40 - £99	352 (40.23) [76]	5.36 (4.28, 6.71)	1.35 (0.85, 2.15)		0.04**
< £40	389 (44.46) [99]	6.33 (5.20, 7.71)	1.60 (1.01, 2.51)		

* p-value from likelihood ratio test ** p-value from test for trend ♦ p-value from test of deviation from linearity

a Follow-up from age at menarche to age 44 years (N = 1,679, no. of hysterectomies = 175)

b Follow-up from age 44 to 57 years (N = 1,457, no. of hysterectomies = 195)

c Follow-up from age at menarche to age 44 years (N = 1,762, no. of hysterectomies = 188)

d Follow-up from age 44 to 57 years (N = 1,523, no. of hysterectomies = 208)

Table 4.3: Survival analyses of the associations between hysterectomy and father's occupational class and maternal education adjusted for each other (N=1,569, no. of hysterectomies=339)

Variables included in the model		Unadjusted Hazard Ratio for hysterectomy (95% CI)	Hazard Ratio for hysterectomy (95% CI) adjusted for other variable
Father's occupational class	I or II	1.00	1.00
	IIINM	1.39 (0.98, 1.99)	1.31 (0.92, 1.88)
	IIIM	1.42 (1.05, 1.91)	1.28 (0.93, 1.76)
	IV or V	1.59 (1.16, 2.16)	1.42 (1.02, 1.98)
	p-value	*0.02*	*0.20*
Maternal education	1 (High)	1.00	1.00
	2	1.69 (1.01, 2.81)	1.62 (0.97, 2.70)
	3	1.87 (1.16, 3.02)	1.68 (1.03, 2.75)
	4 (Low)	1.86 (1.23, 2.81)	1.61 (1.04, 2.50)
	p-value	*0.01*	*0.13*

Maternal education: 1 = Secondary and further or higher education ; 2 = Secondary only or Primary and further or higher education ; 3 = Primary and further education (no qualifications) ; 4 = Primary education only

Table 4.4: Survival analyses of the associations between maternal education, father's occupational class and hysterectomy adjusted for educational level and adult head of household occupational class (N=1,492, no. of hysterectomies=324)

Indicator of SEP		Unadjusted Hazard Ratio for hysterectomy (95% CI)	Hazard Ratio for hysterectomy (95% CI) adjusted for education†	Hazard Ratio for hysterectomy (95% CI) adjusted for head of household occupational class†	Fully adjusted* Hazard Ratio for hysterectomy (95% CI)
Father's occupational class					
	I or II	1.00	1.00	1.00	1.00
	IIINM	1.18 (0.82, 1.72)	1.14 (0.78, 1.66)	1.17 (0.81, 1.70)	1.14 (0.78, 1.65)
	IIIM	1.37 (1.02, 1.86)	1.21 (0.88, 1.68)	1.32 (0.97, 1.80)	1.20 (0.87, 1.67)
	IV or V	1.51 (1.10, 2.06)	1.33 (0.95, 1.87)	1.44 (1.04, 1.98)	1.32 (0.93, 1.85)
	p-value	*0.05*	*0.43*	*0.14*	*0.47*
Maternal education	1 (High)	1.00	1.00	1.00	1.00
	2	1.74 (1.03, 2.92)	1.65 (0.98, 2.79)	1.72 (1.02, 2.90)	1.66 (0.98, 2.80)
	3	1.85 (1.13, 3.01)	1.64 (1.00, 2.71)	1.80 (1.10, 2.94)	1.64 (1.00, 2.71)
	4 (Low)	1.81 (1.19, 2.76)	1.51 (0.96, 2.37)	1.71 (1.11, 2.63)	1.48 (0.94, 2.33)
	p-value	*0.03*	*0.18*	*0.06*	*0.18*

Maternal education: 1 = Secondary and further or higher education ; 2 = Secondary only or Primary and further or higher education ; 3 = Primary and further education (no qualifications) ; 4 = Primary education only

* Adjusted for education and adult head of household occupational class

† entered into models as a time varying covariate

Table 4.5: Survival analyses of the associations between hysterectomy and maternal education, education and adult head of household occupational class adjusted for each other (N=1,513 no. of hysterectomies=152) (Follow-up to age 44 years)

Indicators of SEP		Unadjusted Hazard Ratio for hysterectomy (95% CI)	Fully adjusted* Hazard Ratio for hysterectomy (95% CI)
Maternal education	1 (High)	1.00	1.00
	2	2.63 (1.08, 6.39)	2.22 (0.91, 5.43)
	3	2.61 (1.11, 6.13)	1.88 (0.78, 4.50)
	4 (Low)	3.00 (1.40, 6.45)	1.85 (0.83, 4.14)
	p-value	*0.01*	*0.31*
Educational level			
	Degree or higher	1.00	1.00
	Advanced secondary	5.63 (0.76, 41.74)	5.20 (0.70, 38.70)
	Ordinary secondary	7.95 (1.09, 58.01)	6.49 (0.87, 48.20)
	Below secondary	13.18 (1.77, 98.00)	10.27 (1.35, 78.39)
	None	10.95 (1.52, 78.75)	8.49 (1.14, 63.09)
	p-value	*0.0001*	*0.01*
Adult head of household occupational class	I or II	1.00	1.00
	IIINM	1.41 (0.86, 2.30)	1.16 (0.71, 1.91)
	IIIM	1.74 (1.20, 2.53)	1.29 (0.87, 1.92)
	IV or V	1.31 (0.77, 2.22)	0.98 (0.57, 1.70)
	p-value	*0.03*	*0.57*

Maternal education: 1 = Secondary and further or higher education ; 2 = Secondary only or Primary and further or higher education ; 3 = Primary and further education (no qualifications) ; 4 = Primary education only

* Adjusted for the other two indicators of SEP shown in the table

Table 4.6: Unadjusted survival analyses of the associations between indicators of SEP in childhood and hysterectomy by reason for hysterectomy in the NSHD

Indicator of SEP	Hazard Ratio for hysterectomy for specified reason (95% CI) [No. of hysterectomies]					
	Fibroids	Menstrual disorders	Prolapse	Cancer	Other	Unknown
Paternal education (N=1580)	[N=107]	[N=99]	[N=35]	[N=26]	[N=52]	[N=29]
1 (High)	1.00	1.00	1.00	1.00	1.00	1.00
2	1.23 (0.65, 2.30)	1.83 (0.78, 4.29)	4.38 (1.21, 15.92)	1.28 (0.08, 20.49)	0.71 (0.24, 2.13)	1.08 (0.33, 3.54)
3	1.05 (0.54, 2.04)	2.15 (0.93, 4.96)	1.89 (0.42, 8.42)	4.17 (0.43, 40.05)	0.77 (0.26, 2.30)	0.93 (0.26, 3.31)
4 (Low)	0.80 (0.48, 1.33)	2.07 (1.03, 4.16)	1.83 (0.54, 6.23)	6.23 (0.84, 46.33)	1.09 (0.52, 2.28)	0.70 (0.27, 1.83)
p-value	*0.40*	*0.15*	*0.08*	*0.04*	*0.74*	*0.81*
Crowding (persons/ room) (N=1788)	[N=124]	[N=115]	[N=38]	[N=26]	[N=60]	[N=35]
≤1	1.00	1.00	1.00	1.00	1.00	1.00
1.1 - 1.9	0.69 (0.43, 1.12)	1.24 (0.80, 1.92)	0.87 (0.38, 2.00)	1.94 (0.80, 4.68)	1.62 (0.90, 2.92)	1.75 (0.84, 3.65)
≥2	0.71 (0.39, 1.30)	1.21 (0.70, 2.08)	1.07 (0.41, 2.79)	2.08 (0.74, 5.85)	1.64 (0.81, 3.33)	1.10 (0.37, 3.21)
p-value	*0.20*	*0.57*	*0.92*	*0.22*	*0.18*	*0.35*
Indoor bathroom (N=1755)	[N=123]	[N=114]	[N=38]	[N=26]	[N=58]	[N=34]
Yes	1.00	1.00	1.00	1.00	1.00	1.00
No	0.47 (0.26, 0.83)	1.41 (0.93, 2.14)	0.34 (0.10, 1.10)	1.19 (0.48, 2.96)	2.23 (1.31, 3.81)	1.42 (0.66, 3.05)
p-value	*0.004*	*0.12*	*0.07*	*0.71*	*0.005*	*0.38*
Running hot water (N=1755)	[N=123]	[N=114]	[N=38]	[N=26]	[N=58]	[N=34]
Yes	1.00	1.00	1.00	1.00	1.00	1.00
No	0.99 (0.64, 1.51)	1.30 (0.86, 1.97)	0.54 (0.21, 1.39)	1.06 (0.42, 2.63)	1.71 (0.99, 2.96)	1.69 (0.82, 3.46)
p-value	*0.95*	*0.22*	*0.17*	*0.91*	*0.06*	*0.17*

Paternal education: 1 = Secondary and further or higher education ; 2 = Secondary only or Primary and further or higher education ; 3 = Primary and further education (no qualifications) ; 4 = Primary education only

Table 4.7: Unadjusted survival analyses of the association between education and hysterectomy by reason for hysterectomy in the NSHD

Educational level	Hazard Ratio for hysterectomy for specified reason (95% CI) [No. of hysterectomies]					
	Fibroids	Menstrual disorders	Prolapse	Cancer	Other	Unknown
Follow-up to age 44 years						
(N=1679)	[N=43]	[N=66]	[N=9]	[N=17]	[N=30]	[N=10]
Degree or higher	1.00	-	1.00	-	-	-
Advanced secondary	2.52 (0.32, 19.70)	1.00*	no hysterectomies	1.00*	1.00*	-
Ordinary secondary	1.82 (0.23, 14.56)	1.64 (0.76, 3.54)	0.68 (0.07, 6.50)	1.13 (0.16, 8.00)	1.28 (0.46, 3.54)	1.00**
Below secondary	3.83 (0.46, 31.82)	2.87 (1.22, 6.75)	1.87 (0.19, 18.01)	1.57 (0.14, 17.32)	1.33 (0.34, 5.14)	3.93 (0.66, 23.49)
None	2.77 (0.37, 20.77)	2.01 (1.00, 4.02)	0.30 (0.03, 3.34)	4.55 (1.02, 20.35)	1.29 (0.51, 3.27)	2.38 (0.57, 9.96)
p-value	*0.53*	*0.08*	*0.07*	*0.05*	*0.95*	*0.28*
Follow-up from age 44 to 57 years						
(N=1457)	[N=72]	[N=39]	[N=27]	[N=9]	[N=28]	[N=20]
Degree or higher	1.00	1.00	1.00	-	1.00	1.00
Advanced secondary	0.84 (0.33, 2.10)	2.12 (0.27, 16.95)	1.86 (0.23, 15.15)	1.00*	1.86 (0.23, 15.08)	1.06 (0.12, 9.48)
Ordinary secondary	0.97 (0.40, 2.38)	2.93 (0.38, 22.56)	2.25 (0.29, 17.76)	3.57 (0.37, 34.35)	0.98 (0.11, 8.80)	1.47 (0.18, 12.23)
Below secondary	1.00 (0.35, 2.87)	2.25 (0.23, 21.67)	no hysterectomies	no hysterectomies	3.77 (0.44, 32.27)	0.75 (0.05, 12.05)
None	0.43(0.17, 1.10)	2.57 (0.34, 19.47)	1.81 (0.23, 14.11)	4.32 (0.50, 36.98)	1.91 (0.25, 14.77)	1.39 (0.17, 11.10)
p-value	*0.07*	*0.79*	*0.24*	*0.26*	*0.35*	*0.95*

* No hysterectomies in baseline group so top two categories combined

** No hysterectomies in either of top two categories so top three categories combined

Table 4.8: Unadjusted survival analyses of the associations between indicators of SEP in adulthood and hysterectomy by reason for hysterectomy in the NSHD

Indicator of SEP	Hazard Ratio for hysterectomy for specified reason (95% CI) [No. of hysterectomies]					
	Fibroids	Menstrual disorders	Prolapse	Cancer	Other	Unknown
Own occupational class (N=1642)	[N=117]	[N=110]	[N=34]	[N=25]	[N=55]	[N=28]
I & II	1.00	1.00	1.00	1.00	1.00	1.00
IIINM	1.05 (0.69, 1.60)	1.03 (0.65, 1.62)	0.61 (0.25, 1.47)	3.27 (0.90, 11.87)	1.14 (0.61, 2.14)	2.25 (0.92, 5.46)
IIIM	0.72 (0.30, 1.69)	1.79 (0.95, 3.37)	0.78 (0.18, 3.48)	6.61 (1.48, 29.55)	0.28 (0.04, 2.08)	1.43 (0.30, 6.89)
IV & V	1.09 (0.66, 1.81)	1.21 (0.72, 2.04)	1.69 (0.76, 3.78)	5.15 (1.37, 19.43)	1.60 (0.81, 3.18)	0.83 (0.21, 3.21)
p-value	*0.80*	*0.34*	*0.17*	*0.02*	*0.15*	*0.18*
Housing (N=1770)	[N=124]	[N=113]	[N=38]	[N=26]	[N=60]	[N=35]
Owner-occupied	1.00	1.00	1.00	1.00	1.00	1.00
Not owner-occupied	0.77 (0.47, 1.28)	0.49 (0.26, 0.91)	0.55 (0.20, 1.56)	2.41 (1.08, 5.41)	2.28 (1.33, 3.91)	1.58 (0.74, 3.38)
p-value	*0.30*	*0.01*	*0.23*	*0.04*	*0.004*	*0.25*
Income (per week) (N=875)	[N=65]	[N=63]	[N=19]	[N=14]	[N=26]	[N=11]
≥£100	1.00	1.00	-	-	1.00	1.00
£40 - £99	0.50 (0.24, 1.04)	1.68 (0.74, 3.84)	1.00*	1.00*	2.66 (0.60, 11.77)	2.86 (0.35, 23.26)
< £40	1.03 (0.54, 1.94)	1.41 (0.62, 3.24)	2.23 (0.88, 5.66)	3.23 (1.01, 10.30)	2.04 (0.45, 9.19)	1.12 (0.12, 10.78)
p-value	*0.03*	*0.42*	*0.08*	*0.04*	*0.35*	*0.28*
Follow-up to age 44 years						
Occupational class of head of household (N=1762)	[N=47]	[N=70]	[N=9]	[N=17]	[N=31]	[N=14]
I & II	1.00	1.00	1.00	1.00	1.00	1.00
IIINM	1.29 (0.61, 2.75)	1.59 (0.73, 3.45)	2.58 (0.43, 15.42)	0.55 (0.07, 4.51)	0.89 (0.25, 3.12)	1.29 (0.26, 6.41)
IIIM	0.60 (0.27, 1.31)	2.46 (1.40, 4.33)	2.65 (0.59, 11.84)	1.99 (0.70, 5.68)	1.68 (0.75, 3.76)	2.00 (0.64, 6.20)
IV & V	0.48 (0.14, 1.57)	2.34 (1.16, 4.72)	no hysterectomies	1.22 (0.25, 5.88)	1.31 (0.43, 4.01)	no hysterectomies
p-value	*0.22*	*0.009*	*0.24*	*0.46*	*0.59*	*0.18*
Follow-up from age 44 to 57 years						
Occupational class of head of household (N=1523)	[N=77]	[N=43]	[N=29]	[N=9]	[N=29]	[N=21]
I & II	1.00	1.00	1.00	1.00	1.00	1.00
IIINM	0.68 (0.32, 1.44)	0.71 (0.25, 2.07)	1.12 (0.37, 3.40)	no hysterectomies	0.26 (0.03, 1.98)	1.07 (0.30, 3.83)
IIIM	0.85 (0.49, 1.47)	0.99 (0.47, 2.09)	1.44 (0.62, 3.33)	1.70 (0.38, 7.58)	0.89 (0.34, 2.29)	1.00 (0.35, 2.87)
IV & V	0.49 (0.19, 1.23)	1.44 (0.61, 3.37)	0.67 (0.15, 2.95)	2.36 (0.43, 12.91)	2.14 (0.87, 5.26)	0.83 (0.18, 3.74)
p-value	*0.33*	*0.72*	*0.73*	*0.30*	*0.10*	*0.99*

* No hysterectomies in baseline group so top two categories combined

Table 4.9: Unadjusted hazards ratios (HR) for hysterectomy comparing worst socioeconomic condition with best for indicators of SEP from across life in three British cohorts using relative indices of inequality

	BWHHS (1920 - 40) N = 3208 Hysterectomy = 705	NSHD (1946) N = 1394 Hysterectomy = 305		Aberdeen (1950 - 55) N = 3208 Hysterectomy = 448
	HR (95% CI)	HR (95% CI)		HR (95% CI)
Childhood SEP				
Father's occupational class	0.73 (0.56, 0.96)	1.77 (1.19, 2.65)		2.06 (1.46, 2.89)
p-value	*0.02*	*0.005*		*< 0.001*
Housing	-	1.58 (0.97, 2.56)		1.74 (1.06, 2.86)
p-value	-	*0.07*		*0.03*
Crowding	-	1.22 (0.77, 1.94)		1.63 (1.14, 2.32)
p-value	-	*0.40*		*0.007*
Shared a bedroom	0.73 (0.41, 1.28)	1.34 (0.85, 2.11)		-
p-value	*0.27*	*0.20*		-
Indoor bathroom	0.62 (0.45, 0.86)	0.90 (0.51, 1.61)		-
p-value	*< 0.001*	*0.73*		-
Running hot water	0.60 (0.46, 0.88)	1.31 (0.77, 2.24)		-
p-value	*0.006*	*0.33*		-
Educational level				
Age at leaving school	0.59 (0.43, 0.81)	**Up to 44 years**[†] 2.12 (1.08, 4.17)	**44 to 57 years**[*] 1.03 (0.56, 1.90)	2.34 (1.62, 3.37)
p-value	*0.001*	*0.03*	*0.93*	*< 0.001*
Highest educational attainment	-	2.45 (1.33, 4.54)	0.95 (0.55, 1.65)	1.90 (1.35, 2.66)
p-value	-	*0.004*	*0.87*	*< 0.001*
Adult SEP				
Own occupational class	0.93 (0.70, 1.23)	1.57 (1.05, 2.37)		1.29 (0.90, 1.86)
p-value	*0.60*	*0.03*		*0.18*
Occupational class of head of household	1.08 (0.82, 1.42)	**Up to 44 years**[†] 2.07 (1.14, 3.76)	**44 to 57 years**[*] 1.10 (0.63, 1.92)	-
p-value	*0.57*	*0.02*	*0.74*	-
Housing	0.75 (0.51, 1.12)	1.26 (0.70, 2.26)		1.26 (0.78, 2.04)
p-value	*0.16*	*0.44*		*0.35*

† Up to age 44 years (N = 1,394, no. of hysterectomies = 141)
* Age 44 to 57 years (N = 1,219, no. of hysterectomies = 164)

Chapter 5: Body weight and hysterectomy

Main objective: To investigate whether body weight at time points across life is associated with subsequent hysterectomy risk.

5.1 Introduction

This chapter examines the influence of body weight at different stages of life on subsequent hysterectomy risk. The relationship between body weight and hysterectomy has been evaluated in a number of existing studies. Although there is some suggestion that women of greater weight may be at increased risk of hysterectomy and that hysterectomy could cause weight gain, the evidence remains unclear and unconvincing and is limited by a strong reliance on cross-sectional studies.

As it has not only been proposed that weight could influence hysterectomy risk but also that hysterectomy could influence subsequent weight, the study of the relationship between weight and hysterectomy is more complicated than the study of relationships which have only one plausible direction of association and is why a reliance on cross-sectional studies has major limitations. Longitudinal studies with measures of body weight both before and after hysterectomy are necessary to identify whether body weight is a predictor and/or a consequence of hysterectomy. A life course perspective is also appropriate and potentially illuminating as weight tracks across life and adult weight is influenced by factors acting from early life onwards.[113;200]

From a public health perspective, a better understanding of the association between weight and subsequent hysterectomy rates would be beneficial - if being overweight or obese does increase risk of hysterectomy we may expect that with the proportion of the population who are obese increasing in countries across the world[200;201] the number of women requiring hysterectomy will increase. Another important benefit is the need to establish the long-term health consequences of hysterectomy so that women can make informed decisions. If hysterectomy is associated with an increased risk of becoming overweight or obese, it may be possible to provide more informed pre- and post-procedural care for women who undergo hysterectomy and define a group who should receive targeted advice about weight. If there is no association this will provide reassurance.

The analyses in this chapter examine whether weight affects subsequent hysterectomy risk, chapter 9 will address the association between hysterectomy and subsequent body weight. As there is so much overlap between studies of weight as a predictor and studies of weight as a consequence of hysterectomy the literature review which follows will summarise the findings from all studies of the association between weight and hysterectomy.

5.2 Literature review

Twenty nine studies[120;122;124-126;129;130;142;144;153-165;202-208] have examined the association between body weight and hysterectomy (for summarised details of studies see appendix 5). Some of these aimed to examine the effect of weight on hysterectomy,[120;126;144;154;162;164;165] others to examine the effect of hysterectomy on weight[202;204-208] with additional studies attempting to investigate effects in both directions.[155;161;203] Further studies have tested for an association without hypothesising about its direction.[122;124;125;129;130;142;153;156-160]

5.2.1 The effect of weight on hysterectomy

Of those studies which aimed to investigate whether weight predicts hysterectomy[120;126;144;154;155;161;162;164;165;203] most found some evidence in support of a positive association, with women of higher weight at increased risk of hysterectomy. Unfortunately a number of factors limit these findings.

Five of the studies[120;126;162;164;165] used a cross-sectional design and so although the authors interpreted their significant findings as evidence that body mass index (BMI), the measure of weight used in all these studies, predicts hysterectomy, as BMI was measured at the time of the study and after hysterectomy, reverse causality is a possible explanation i.e. the results could as easily be explained by an association acting in the opposite direction (i.e. hysterectomy predicting subsequent BMI). The same problem exists in interpreting the results of the association between BMI measured at baseline and prevalent hysterectomies in Settnes and colleagues' study.[154] This study also collected retrospective information on BMI at age 25 years, weight fluctuations across adult life, dieting habits and having overweight relatives and so has advantages over the cross-sectional studies. Further, Settnes and colleagues followed-up the women who had not had hysterectomy at the initial examination when BMI was measured to create a second analysis of incident hysterectomies from which it was possible to establish a clear temporal relationship between weight and hysterectomy.[154] A fifth cross-sectional study[144] published recently, found no association between hysterectomy and waist:hip ratio measured at the time of the study but did find an association between hysterectomy and increases in weight of >5kg in the 5 years prior to the study although as for the other cross-sectional studies the temporal nature of these associations cannot be established. In an attempt to overcome this problem Ceausu and colleagues[144] used a similar method to that employed by Settnes and colleagues in their prevalence study and study participants were asked to recall their weight at age 25 years. When the association between this measure of weight in earlier adulthood and hysterectomy was tested it was found that women who had greater weight at age 25 years had greater risk of hysterectomy. However, this study failed to adjust for the height of the participants or important confounders which are important limitations.

Three other studies have tried to establish a clear temporal relationship between weight and subsequent hysterectomy risk.[155;161;203] Two of these studies plus the study of incident hysterectomies by Settnes and colleagues[154;155;203] were prospective cohorts, women were enrolled and their weights measured prior to hysterectomy which then occurred during follow-up, the fourth study[161] collected measures of pre-hysterectomy weight retrospectively. Hjortland and colleagues[155] found that women who went on to have a hysterectomy with bilateral oophorectomy were heavier than their controls, whereas women who went on to have a hysterectomy with a unilateral or no oophorectomy or who had a natural menopause were not significantly heavier than their controls. However there was no control for confounding, which is an important limitation. In Settnes and colleagues' incidence study[154] unstable weight across adult life was significantly associated with hysterectomy after control for confounders but, this measure was self-reported retrospectively and is therefore limited. In the third prospective study[203] Sowers and colleagues found little difference in weight, BMI, body fat percentage or waist:hip ratio when comparing women who were still menstruating at the end of follow-up with those who had had a hysterectomy, however, these differences were not formally tested, sample sizes were small and there was no control for confounding. In a retrospective analysis by

Kirchengast and colleagues[161] women who went on to have a hysterectomy had higher pre-menopausal mean body weight than their comparison group but this difference was not significant. In this study the method used to collect the pre-menopausal weight of the comparison group (retrospective self-report) was different to that used to collect pre-hysterectomy weight (clinical records), absolute weight rather than a relative measure or a measure adjusted for height was used and there was no control for confounding.

5.2.2 Plausibility of weight predicting hysterectomy

In using the term weight, epidemiologists usually implicitly mean adiposity (i.e. degree of 'fatness'), as is the case in this thesis also. In assessing the plausibility of the association between weight and subsequent hysterectomy, it is therefore necessary to consider the underlying biological and social processes which could explain an association between levels of body fat, gynaecological health and subsequent hysterectomy. Unfortunately few authors have made attempts to explain the relationships they are proposing or have found. Of those that have, one common suggestion is that weight may influence hysterectomy risk because of the relationship between weight and the development of gynaecological disorders which are common reasons for hysterectomy.[154;162] This is supported by evidence from studies of the association between body weight from childhood onwards and gynaecological outcomes which have found that women who are overweight or obese have higher risk of developing fibroids,[20] endometrial[209-212] and other gynaecological cancers[213;214] and menstrual problems[201;215;216] than women of normal weight. The most frequently proposed explanation of these findings is the 'unopposed oestrogen' hypothesis.[20;210;211;213;217;218] Adipose tissue converts adrenal androgens to oestrogen whereby the more adipose tissue a woman has, the greater amount of oestrogen she produces. This increased production of oestrogen coupled with the fact that women who are overweight or obese tend to have reduced levels of sex hormone binding globulin, results in these women having higher levels of unopposed oestrogen, which promotes the development of many gynaecological disorders including fibroids and cancer.

For some gynaecological outcomes, women who are underweight also have an elevated risk. There is evidence that women who are either underweight or overweight are more likely to have infertility problems,[201;216;219;220] be subfertile (i.e. have delayed conception rates),[221;222] experience miscarriage[215] and suffer from menstrual irregularities[201;215;216;221] than women of normal weight possibly because women at both extremes of body weight are at greater risk of disruptions to their endogenous hormone levels. Highlighting the need to take a life course perspective, many of these J-shaped associations are found when the effects of weight not only in adulthood but also in childhood and late adolescence are examined.[216;221] Further, weight gain and instability in weight over time have recently been shown to predict gynaecological outcomes.[223;224]

Given these findings, an association between weight at time points across life and subsequent hysterectomy risk therefore seems plausible.

5.2.3 The effect of hysterectomy on subsequent weight

Prior to the mid-1970s the only evidence of the effect of hysterectomy on subsequent weight was from studies without comparison groups,[225-227] which given all women have a tendency towards increasing weight and greater fat composition as they age regardless of their hysterectomy status[201] is unsatisfactory in terms of assessing whether hysterectomy does influence weight or body composition. Since 1976 when the first study[155] to examine the influence of hysterectomy on weight using appropriate methods was conducted, several other studies[161;202-208] have also aimed to examine the influence of hysterectomy on weight or body composition. These studies do not provide strong evidence that hysterectomy influences weight even though in studies of women's subjective perceptions of the effect of their hysterectomies many think their hysterectomy has caused subsequent weight gain.[228;229] While some studies[161;206;207] have found that hysterectomised women were heavier than other women, other studies[155;202;204;208] have found no association.

There are limitations to these studies. Firstly, three of the studies,[206-208] two of which found a positive association were cross-sectional. These studies, as for the cross-sectional studies which attempted to assess the effect of weight on hysterectomy, were greatly limited by the problem of reverse causality.

The only other study[161] to find a clear positive effect, found that women who had a hysterectomy had higher BMI, gained significantly more weight and had significantly more fat tissue especially in the abdominal region than their naturally menopausal comparison group. Kirchengast and colleagues did have measures of pre- and post-hysterectomy weight and pre- and post-menopausal weight for the comparison group, but body composition was only measured after hysterectomy and so there is no way of identifying whether women who went on to have hysterectomy had more fat tissue pre-procedure, making reverse causality a problem in interpreting the results on body composition. In addition, the same problems exist for these analyses, as existed for analyses by the same researchers of the effect of weight on hysterectomy - the weight measures were not all taken using the same method (pre- and post-procedure weights were measured using different methods) and, analyses were not adjusted for potential confounders.

In another study[203] the focus of analyses was on the effect of oophorectomy and the data on hysterectomy presented are difficult to assess. There appeared to be no difference in weight or body composition change between the women who had hysterectomy during follow-up and those who continued to menstruate although this was not tested formally, possibly because statistical tests would have had very limited power to detect an effect as the number of women who had a hysterectomy during follow-up was low (n=16).

Another study[205] is difficult to interpret because there was no 'healthy' comparison group. Women who had a hysterectomy were compared with women who had a bilateral salpingo-oophorectomy (removal of ovaries and fallopian tubes) and no difference in body composition three months post-procedure was found. In addition to the lack of a useful comparison group, sample size was small (n=29) and follow-up time was short.

The studies[155;202;204;208] which found little or no evidence of an effect of hysterectomy on weight are also limited. One is a cross-sectional study.[208] Another, a case-control study,[204] found no difference in mean BMI between cases and controls after adjusting for age and time since hysterectomy. However, it is unclear how controls were selected and so the level of bias cannot be assessed. Cohort designs were employed in the other two studies.[155;202] In one of these studies[202] the comparison group was men, which given their different body compositions, hormonal profiles and patterns of changing weight over time may not be appropriate. Hjortland and colleagues[155] used pre-menopausal women as the comparison group which is more appropriate but the analyses were limited by their lack of control for confounders.

5.2.4 Plausibility of hysterectomy predicting weight

As for the association between weight and subsequent hysterectomy risk, few authors have attempted to explain how hysterectomy may influence subsequent weight highlighting the need for further study of the processes underlying these associations. It has been suggested that hysterectomy could result in a period of illness during which time muscle and bone mass are lost and so body fat percentage increases,[206] however, whether this would cause any more than a transient increase in weight, with body fat percentage reducing again once women have recovered from the surgery is not clear. Another suggestion is that hysterectomy could cause psychological stress, possibly related to loss of fertility and femininity, which results in women who undergo such a procedure increasing their calorie intake and reducing their activity levels.[161] Further, even without oophorectomy, hysterectomy could affect oestrogen production which it has been proposed could influence subsequent weight and body composition.[161] Another possibility is that as abdominal hysterectomies, the most common form of the procedure, involve making large incisions in the abdomen this could disrupt the anatomy of this region of the body and damage muscle and fat tissue causing detrimental changes in weight and body composition or negatively affecting body image leading to reductions in women's activity levels.

5.2.5 Studies with no proposed direction of association

Several other cross-sectional studies[122;124;125;129;130;142;153;156-160] tested whether there was an association between weight and hysterectomy without proposing a direction of association. Most of these found some evidence of a positive association,[124;125;142;153;156;157;160] although some of these did not retain significance after control for confounders.[125] The major limitation of these studies as for the similar studies detailed earlier is that they were cross-sectional and so with the exception of one study[153] which measured BMI in the week before surgery, it is not possible to establish in what direction the associations act.

5.2.6 General appraisal of published studies

5.2.6.1 Countries of study

Studies of the association between weight and hysterectomy have been conducted in a range of countries, the majority in the USA.[120;122;125;129;130;142;155;158;159;203;205;206;208] No studies, with the exception of a previous analysis in the NSHD,[163] have included British women. There is wide variation in rates of hysterectomy between countries,[104] it would therefore be informative to examine in detail whether a relationship between weight and hysterectomy is evident in British women.

5.2.6.2 Definition of hysterectomy

There is no consistency in the types of hysterectomy included in different studies. A range of definitions and inclusion criteria are employed from that used by Kirchengast and colleagues which is very specific (e.g. 'hysterectomy using the abdominal route for a non-malignant purpose with at least one ovary conserved')[161] through to the other extreme of including all hysterectomies for whatever reason which most studies have done.[122;124;125;129;142;144;156;159;160;165;202;204;207] Between these two extremes are a number of studies which have included only hysterectomies performed for benign reasons,[126;153;154] another which included only total abdominal hysterectomies[205] and four which included only pre-menopausal hysterectomies.[153;157;162;164] Other studies grouped together women with hysterectomy with women who had undergone only an oophorectomy.[125;203;206;208] Given the predictors and consequences of hysterectomy may vary dependent upon the reason for the procedure and whether ovaries were also removed grouping all malignant and benign indications and all oophorectomies and hysterectomies together may dilute any specific effects. This highlights the need to carefully consider the inclusion criteria used and categorisations made when assessing the associations between weight and hysterectomy in both directions.

5.2.6.3 Measurement of weight

There are a number of methods of approximating adiposity and distribution of fat using measures of body weight and composition. Unfortunately it tends to be that the more accurate the method of estimation, the greater are the logistical problems in using it to measure large cohorts of people.[200;230] It is thus often necessary for researchers to find a simple measure which does not have too many limitations. One of the simplest measures, absolute weight is unsatisfactory for use in epidemiological studies as it is correlated not only with adiposity but also height. Instead, measures of weight adjusted for height tend to be calculated, the most frequently used of which is BMI (weight(kg)/[height (m)]^2). Measures of weight adjusted for height do have limitations including the fact that no distinction is made between muscle and fat whereby muscular people may have high BMI despite having low levels of body fat. However, because height and weight are easily collected they are often used in preference to direct measures of body fat such as skinfold thickness or more accurate measures of body composition such as dual x-ray absorptiometry which can only be measured by trained professionals using specialist equipment and are expensive.[200;230]

Literature searches aimed to identify studies which examined any measure of weight or body composition, however, supporting the notion that BMI is the most commonly used measure, most studies had used BMI. While using BMI is not necessarily a limitation, most studies considered BMI at only one time point or at time points only in middle-age which is unsatisfactory from a life course perspective. A number of analyses were limited further by considering only mean BMI or categorising BMI into only two groups which does not allow for the fact that the relationship between weight and hysterectomy may be complex. Other measures considered include: weight;[144;157] relative weight;[155] BMI or weight at age 25 years;[144;154] stability of weight across adult life;[154] increases in weight over a 5-year period;[144] having been on slimming diets;[154] waist:hip ratio;[144;159;163;203;205] body fat percentage;[161;203;205] amount of body fat at various sites;[157] and fat:lean ratio.[161;203] In the only two studies to consider weight change and weight in earlier adulthood[144;154] there was evidence that weight cycling across adult life (defined as a self-report of a weight gain or loss of more than 5kg not due to pregnancy during adulthood) was a more important determinant of hysterectomy than high BMI[154] and that increases in weight were associated with hysterectomy.[144] This suggests that using a life course approach and considering weight/body composition at time points across life rather than only in middle-age may be informative in studies of the association between hysterectomy and weight.

A limitation of many studies was that height and weight measures were self-reported. Various studies[231-234] have shown that women tend to underestimate their weight and overestimate their height with differential misclassification by BMI whereby women who are overweight or obese are more likely to underreport their weight than other women. Using such measures will have resulted in levels of overweight and obesity in populations being underestimated and could have introduced bias.

5.2.6.4 Age range of study populations and sample size

In many studies the age range of women included spanned at least two decades. Grouping these women together, while increasing sample size and hence statistical power, may, if appropriate consideration is not made in statistical models have diluted the size of any cohort-specific effect, which as the cross-cohort comparisons in the previous chapter demonstrate are possible. Further, some studies included only small numbers of women and so may have had insufficient power to detect an appropriate level of effect.

5.2.7 Summary of findings from the literature review

From the literature review it can be seen that existing studies have found either a positive or no association between weight and hysterectomy, with results suggesting that this relationship, if it really exists, could be acting in either or both directions. However, the evidence is weak and unconvincing. Many studies have used designs which make it difficult to assess the temporal relationship and even among those studies that do employ appropriate designs there are a number of problems which limit generalisability and make it difficult to draw any conclusive statements about the nature of the relationship. The need for further study which the findings of the literature review support, is acknowledged by Matthews and colleagues[206] authors of one of the most recent studies. This need is especially true when taking a life course perspective as few studies have made consideration of weight at time points other than immediately proceeding and preceding treatment which may not be when the effect of weight on hysterectomy or of hysterectomy on weight is most influential.

5.2.8 Previous work using data from the NSHD

The relationship between hysterectomy and weight in the NSHD was briefly investigated in a recent paper examining the influence of menopausal status on cardiovascular risk factors.[163] As well as examining other cardiovascular risk factors Kuh and colleagues investigated differences in BMI, waist circumference and waist:hip ratio between women in different menopausal groups at age 53 years, one group of which was hysterectomised women not taking hormone replacement therapy (HRT). At age 53 years women who had undergone a hysterectomy who were not taking HRT had increased BMI and waist circumference compared to other menopausal groups. However, adjustment for SEP and BMI/waist circumference at age 43 years reduced this association leading the authors to propose that hysterectomised women were already more overweight or obese at age 43 years. This suggests the possibility of an association but, as BMI was considered at only two time points in middle-age, and the association in only one of the two possible directions was assessed, this requires further and more detailed investigation.

5.3 Specific objectives of the chapter

The specific objectives to be addressed in this chapter are:

i. to examine whether BMI at different time points across life is associated with subsequent hysterectomy rates
ii. to examine whether changes in BMI across life are associated with subsequent hysterectomy rates
iii. to examine whether the associations between BMI and subsequent hysterectomy rates differ by reason for hysterectomy

5.4 Methods

5.4.1 Main outcome variable

Hysterectomy with or without oophorectomy

5.4.2 Main explanatory variables

BMI at ages 2, 4, 6, 7, 11, 15, 20, 26, 36, 43 and 53 years.

5.4.3 Measure of weight

The measurement of adiposity selected needed to be available at time points across life. As many of the more accurate measures of body fat and composition have only been introduced in recent years, cohorts already in adulthood, including the NSHD, do not have such measures available from early life. Weight adjusted for height therefore tends to be the most appropriate of the available estimates of adiposity to use when repeated measures across life are required.

As weight and height were available at all major data collection points in the NSHD and BMI, as previously discussed, is considered to be a good proxy measure of adiposity[200] this was the measure used. At all ages, except ages 20 and 26 years when height and weight were self-reported, height and weight were measured using standardised protocols and equipment by health professionals. In childhood and adolescence height and weight were measured by school doctors or nurses while the study participants were wearing only their underclothes.[235] At ages 36, 43 and 53 years height and weight were measured during physical examinations performed by specially trained nurses at the study participants' homes. Height without shoes was measured to the nearest 0.5cm and weight in light indoor clothing was measured to the nearest 0.5kg. 0.5kg was subtracted from the measured weights of women to correct for clothes worn.[236] Women were not measured if they were pregnant at the time of assessment. The accuracy of the self-reported heights and weights at ages 20 and 26 years have been assessed.[235] Although there is some evidence that the self-reported measures have led to an underestimation of the prevalence of overweight and obesity at these two ages systematic adjustment of the values was considered unjustified.[235]

5.4.4 Categorisation of BMI

Standard definitions of BMI categories were created for BMI at ages 20 years and above. These categories are: underweight (BMI < 20 kg/m^2), normal weight (20 – 25 kg/m^2), overweight (25 -30 kg/m^2) and obese (BMI > 30 kg/m^2).[200] In childhood and adolescence there are no such definitive cut-points because of the rise in BMI with age even if adiposity is constant.[200] For this reason, age-specific cut-points proposed by Cole and colleagues were used (shown in table 5.1).[237] As Cole and colleagues provide no definition of underweight and only a small number of women were expected to be in this category, normal weight and underweight were grouped together. The categories of BMI at each age in childhood and adolescence were therefore: underweight/normal weight; overweight; obese.

5.4.5 Analyses

In this chapter, because the main aim of analyses was to test the effect of BMI on subsequent hysterectomy risk all women who had a hysterectomy prior to a BMI measurement were excluded from analyses of BMI at that age (e.g. women who had had a hysterectomy at age < 43 years were excluded from analyses of BMI at age 43 years).

5.4.5.1 Analyses to address objective (i) – unadjusted associations

Cox's proportional hazards models were used to test the unadjusted association between BMI at each age of measurement and subsequent hysterectomy rates. In the first set of models BMI was entered as a categorical variable with normal/underweight defined as the baseline group in childhood and adolescence and normal weight defined as the baseline group in adulthood.

Tests of deviation from linearity were then performed firstly by comparing a model with BMI entered as a categorical variable to a model with BMI entered as a linear variable using a likelihood ratio test. Then, a model with BMI entered as a continuous variable with a quadratic BMI term included was run and, tests performed to check whether this quadratic term was statistically significant. Where there was no evidence of deviation from linearity (i.e. in the first test the linear variable fit the data most appropriately and in the second test the quadratic term was not significant), tests for trend were performed on the categorical BMI variable and BMI was entered individually into another model as a continuous variable. Where there was evidence of deviation from linearity, BMI was centred at 20 and a quadratic BMI term was included in models of BMI as a continuous term. BMI was centred for ease of interpretation of the regression coefficients[238] - without centring, the intercepts of the regression model would be at a BMI value of 0 which is not meaningful. BMI was centred at 20 as this represents a normal BMI for women.

In the survival analyses described above no allowance was made for the fact that the time between BMI measurement and hysterectomy had a much greater range at earlier ages of BMI measurement e.g. the model of the association between BMI at age 26 years and hysterectomy included hysterectomies performed between ages 26 and 57 years whereas the model of the association between BMI at age 53 years and hysterectomy only included hysterectomies performed between ages 53 and 57 years. To take account of this and examine whether BMI at a specific age was a good predictor of all subsequent hysterectomies or was a better predictor of hysterectomies performed in the time period immediately after its measurement time-updated analyses of the association between BMI in adulthood and hysterectomy were performed. As there was some evidence that the association between BMI and hysterectomy was non-linear at most ages in adulthood quadratic terms were included when BMI was modelled as a continuous variable. Also, as the nature of the association changed over time, time-updated analyses were run updated only to age 43 years.

The regression equation used for the time-updated analyses when BMI was entered into the model as a continuous variable was:

$$\log h_i(t) = \alpha(t) + \beta_1 x_{i1}(t) + \beta_2 x_{i2}(t)$$

The hazard at time t depended on the values of x_1 and x_2. x_1 in this instance was BMI and x_2 was BMI^2 where BMI was centred at 20. As there were not measures of BMI at the time of every hysterectomy event approximations were used. Up to age 36 years x_1 was taken to be BMI at age 26 years. Between ages 36 and 43 years x_1 was taken to be BMI at age 36 years. Above age 43 years x_1 was taken to be BMI at age 43 years.

SAS was used to perform the time-updated analysis. Women were included if: they had complete data on hysterectomy AND ((complete data on BMI at ages 26, 36 and 43 years) OR (had a hysterectomy or were censored before age 36 years and had complete data on BMI at age 26 years) OR (had a hysterectomy or were censored before age 43 years and had complete data on BMI at age 26 and 36 years) (N = 1,327, no. of hysterectomies = 307)).

5.4.5.2 Analyses to address objective (ii) – weight change

Two periods across life were identified as times when change in BMI with age may predict hysterectomy rates. The first of these was change in BMI during childhood and adolescence, the time when much gynaecological development and, sexual maturation occurs. The second was change in BMI between early and later adulthood which was suggested by findings from two other studies.[144;154]

To model the effect of BMI change between two ages Cox's proportional hazards models were run which included BMI at both ages of measurement. This method was appropriate because as Lucas and colleagues[239] have described,

'..early size adjusted for later size is a measure of change in size between the earlier and later measurement.'[239] (p.246)

For each change in BMI considered a set of three models were run. All three models were performed using the same N with only those women with complete data on both relevant BMI measures and hysterectomy included. Further, as these analyses were testing the effect of BMI change on subsequent hysterectomy rates women were excluded from analyses if their hysterectomy was performed at an earlier age than the age of the later of the two BMI measurements.

Firstly, two unadjusted models were run with BMI at each of the two ages entered as continuous variables into models by themselves. A third model with BMI at both ages included was then run. If there was evidence from the two unadjusted models that the association between BMI at a particular age and hysterectomy was non-linear, BMI at that age was centred at 20 (for the same reasons described previously) and a quadratic BMI term was included. (It could not be assumed that these analyses would produce associations with the same shape as previous unadjusted analyses as they excluded more women and so had a lower N). BMI at ages 2 and 7 years were used to assess the effect of change in BMI in childhood and BMI at ages 7 and 15 years were used to consider the effect of BMI change over adolescence. BMI at age 53 years was used as the later measure in models of BMI change over later adulthood with BMI at ages 36 and 43 years considered in separate sets of models as the earlier measure. To assess the effect of BMI change in earlier adulthood models with BMI measures taken at 43 and 36, 43 and 26, 36 and 26, 36 and 20, 26 and 20 and 26 and 15 years were run. When examining BMI change across earlier adulthood, in addition to running analyses including all women with hysterectomies performed after the age of the later of the two BMI measurements, analyses were also performed restricted to those hysterectomies performed before age 43 years. This was to examine whether there were differences in effect dependent on whether all hysterectomies or only those performed at earlier ages were considered.

5.4.5.3 Analyses to address objective (iii) – reason for hysterectomy

Using the competing risks framework described in chapter 3 the association between BMI at each age and subsequent hysterectomy rates by reason for hysterectomy was assessed. As in the unadjusted analyses described above, BMI at each age was entered in a first model as a categorical variable and in a second model as a continuous variable. In analyses including BMI as a continuous variable, quadratic terms were included at ages where there was evidence from unadjusted analyses that the relationship between BMI at that age and subsequent rates of hysterectomy for all reasons was non-linear.

5.5 Results

5.5.1 Results from analyses to address objective (i) - unadjusted associations

No significant associations between childhood BMI and subsequent hysterectomy rates were found, table 5.1. As figure 5.1 demonstrates women who subsequently had a hysterectomy followed very similar weight trajectories through childhood to women who did not have a hysterectomy.

BMI in adolescence, table 5.1, and adulthood, table 5.2, was significantly associated with subsequent hysterectomy rates. In models of the association between hysterectomy and BMI from ages 11 to 43 years, there was evidence that the associations deviated from linearity. The shape of this effect was n-shaped - women classified, at ages 11, 15, 20, 26, 36 and 43 years, as underweight, had lower rates of hysterectomy than those women classified as normal or overweight at these ages, for example, women who had a BMI at age 26 years of less than $20kg/m^2$ had subsequent rates of hysterectomy 35% lower than women who had a BMI between 20 and 25 kg/m^2. Women classified as obese at these ages were also found to have lower rates of hysterectomy compared to normal and overweight women, and at ages 11, 15, 20 and 26 had lower rates of hysterectomy than underweight women, for example, women who had a BMI at age 26 years of greater than $30kg/m^2$ had subsequent rates of hysterectomy 53% lower than women who had a BMI between 20 and 25 kg/m^2. Figures 5.2 to 5.4 show the shape of these estimated relationships at ages 26 to 43 years. They also demonstrate how the relationship between hysterectomy and BMI at later ages begins to tend towards linearity with women who were obese at ages 36 and 43 years experiencing similar rates of hysterectomy to women who were normal weight and overweight at these ages. This change in the shape of the effect of BMI measured at increasing ages continued and BMI at age 53 years was found to have a positive linear association with subsequent hysterectomy rates, figure 5.5 – for each 1kg/m^2 increase in BMI at age 53 years there was a 7% increase in subsequent rates of hysterectomy whereby women who had a BMI at age 53 years greater than 30kg/m^2 had subsequent rates of hysterectomy two and a half times higher than women who had a BMI between 20 and 25 kg/m^2. The change in the shape of association cannot be explained by women who were obese in adolescence and early adulthood delaying their hysterectomies until later ages relative to other women as all proportional hazards assumptions were valid - for each BMI measurement there was no significant change in the size or direction of the association over time. This suggests that weight change over time may be an important predictor of hysterectomies performed at later ages with women whose weight increases across adulthood i.e. who were normal weight in early adulthood but become overweight or obese in later adulthood experiencing higher subsequent rates of hysterectomy.

The results from the time-updated analyses showed that when updated over time BMI measured at the time point immediately prior to hysterectomy had a significant non-linear effect on subsequent hysterectomy rates (p-value for quadratic term=0.02) suggesting that the non-linear relationship between BMI in early adulthood and subsequent hysterectomy rates was non-linear whether only those hysterectomies in the time period immediately after BMI measurement or all hysterectomies across the remainder of adulthood were considered.

5.5.2 Results from analyses to address objective (ii) - weight change

No effect of BMI change across childhood or adolescence on subsequent hysterectomy rates was found (results not shown).

The results from analyses to assess the effect of BMI change between later ages in adulthood on subsequent hysterectomy rates, table 5.3, found that BMI at ages 53, 43 and 36 years were all positively associated with hysterectomies performed after age 53 years when included in models by themselves. In a model in which BMI at ages 53 and 43 years and a model in which BMI at ages 53 and 36 years were adjusted for each other the hazards ratios of hysterectomy for BMI at age 53 years increased whereas those for BMI at the younger age reduced and changed direction, for example, after adjustment for BMI at 36 years, the hazard ratio of effect of BMI at 53 years increased from 1.08 to 1.21 whereas after adjustment for BMI at 53 years, the effect of BMI at 36 years reduced from 1.05 to 0.82. This suggests that for a given BMI at age 36 or 43 years, higher BMI at age 53 years (i.e. an increase in BMI between the two ages) was associated with increased rates of hysterectomy. The association between change in BMI between age 36 and 53 years and subsequent hysterectomy is statistically significant (p=0.008) providing evidence that increases in BMI occurring in early middle-age may be an important predictor of subsequent hysterectomy rates.

An equally clear association was not found when assessing BMI change in earlier adulthood (results not shown). The hazards ratios of hysterectomy for BMI at 43 years were not altered greatly after adjustment for BMI at 36 or 26 years, whereas adjustment for BMI at age 43 years reduced the hazards ratios of hysterectomy for BMI at 36 and 26 years. This suggests that BMI at age 43 years was a better predictor of subsequent hysterectomy rates (i.e. those performed after age 43 years) than BMI measured earlier in adulthood.

The association between BMI at age 36 years and subsequent hysterectomy rates lost significance after adjustment for BMI at age 26 years suggesting that when BMI at 26 years is known adding BMI at 36 years to the model provides no further information about the relationship with hysterectomy. However, when adjusted for BMI at age 20 years, BMI at 36 years did remain significantly associated with subsequent hysterectomy rates. The specific importance of BMI at age 26 years was highlighted by results which showed that adjustment for BMI at neither 20 nor 15 years greatly altered the hazards ratios for BMI at 26 years while the hazards ratios for BMI at 20 and 15 years were reduced and were no longer significant after adjustment for BMI at age 26 years.

The above results were difficult to compare with each other because the effects considered applied to hysterectomies occurring over differing ranges of age. However, analyses restricted to hysterectomies performed prior to age 43 years (results not shown) were difficult to interpret as the number of hysterectomies included in analyses was reduced to the point where none of the analyses had sufficient power.

5.5.3 Results from analyses to address objective (iii) – reason for hysterectomy

There was no clear pattern of association between BMI in early childhood (from age 2 to 7 years) and rates of hysterectomy for any one category of reason, table 5.4. This suggests that the finding of no association between BMI in early childhood and rates of hysterectomy for all reasons was not masking an association between BMI at younger ages and hysterectomy which was specific to hysterectomies for only one or a few reasons.

In adolescence and adulthood there were no clear differences in the pattern of association between BMI at a particular age and hysterectomies for different categories of reason, tables 5.5 and 5.6. Further, there was no consistent association between hysterectomies for one particular reason and BMI at different ages e.g. although a strong positive, linear association between hysterectomies for cancer and BMI at later ages emerged, BMI at earlier ages was not associated with hysterectomies for cancer in the same way.

5.6 Discussion

5.6.1 Main findings

There was no evidence that BMI at any age in childhood was associated with subsequent hysterectomy rates. However, measures of BMI in adolescence and across adulthood were associated with hysterectomy rates, although this relationship was complex. The relationship between BMI in adolescence and early adulthood and subsequent hysterectomy rates was n-shaped - women who were normal weight had higher rates of subsequent hysterectomy than women who were underweight or obese at these ages. However, the effect of BMI on subsequent hysterectomy rates was not the same at all ages of BMI measurement in adulthood. The association between BMI in later adulthood and subsequent hysterectomy rates was positive and linear - the greater the BMI at age 53 years the greater the subsequent rates of hysterectomy. It was also found that increases in BMI between early and late adulthood were associated with increased rates of subsequent hysterectomies (i.e. those performed after age 53 years). There were no important differences in association by reason for hysterectomy.

5.6.2 Comparison with other studies

The results from these analyses present a more complicated picture of the association between body weight and subsequent hysterectomy risk than has been found in other studies. This is possibly because this is the first study which has used measures of BMI taken prospectively across life and, also had data which because of its temporal nature enabled separation of the effect of weight on hysterectomy from the effect of hysterectomy on weight in analyses.

The only two other studies[144;154] which have assessed the effect of body weight in earlier adulthood on hysterectomy risk found positive associations, which is different to the n-shaped association found in these analyses, these studies do however, support the finding in this study that increases in weight across adult life may be important. One possible reason for differences in findings is that the measures of weight in earlier adulthood used in these other two studies may be unreliable as they were recalled by women once they had reached middle-age rather than collected prospectively.

5.6.3 Explanation of findings

As a caveat, there are limits to how far the results from this chapter should be interpreted given analyses were unadjusted, a limitation which will be addressed in chapter 7. However, even without adjustment for other variables the findings from these analyses are informative.

If body weight was associated with subsequent hysterectomy rates through its influence on the development of gynaecological disorders (as in figure 5.6(i)), possibly through its effect on levels of unopposed oestrogen, it would have been expected that women with higher BMI in adolescence and early adulthood would have experienced the highest rates of hysterectomy, especially for reasons such as fibroids and cancer whose risks of development are associated with lifetime exposure to oestrogen. As there were not positive, linear associations between BMI at younger ages and subsequent hysterectomy rates and no clear differences in association by reason for hysterectomy this pathway would appear not to operate in the NSHD. More generally, the lack of differences in association by reason for hysterectomy despite the fact that increased weight from early adulthood onwards increases risk of the development of some gynaecological disorders such as fibroids[20] and cancer[209;213;214;240] but reduces risk of the development of others including endometriosis,[241-243] suggests that any influence of weight on subsequent hysterectomy risk is not acting directly or exclusively on medical need.

Another possibility is that gynaecological disorders develop and either suffering from the symptoms of these limit women's activity levels, the disorder disrupts hormone levels and/or the disorders are treated first with less invasive therapies all of which could have detrimental influences on body weight. If any of these pathways is operating an association between weight and subsequent hysterectomy could be found because weight at the time measured is indicating existing gynaecological disorders (see figure 5.6(ii)). If this was the underlying process explaining the association between weight and hysterectomy it would be expected that higher weight and increases in weight would be associated with hysterectomy rates. While this pathway could therefore explain the association between weight at later ages, increases in weight between ages 36 and 53 years and subsequent hysterectomy rates it is an unlikely explanation of the n-shaped association between BMI in earlier adulthood and subsequent hysterectomy rates.

More likely is that the association between BMI and subsequent hysterectomy is mediated by one or more other factors (see figure 5.6(iii)). One such factor is parity. As mentioned in the literature review, it has been shown that women who are at either extreme of body weight in late adolescence and early adulthood are at increased risk of suffering from infertility or subfertility[216;219-221] whereby women who have very high or low BMI in early adulthood are more likely to be nulliparous for the remainder of their lives than other women. The relationship between parity and weight does however change with increasing age as women who by the end of their reproductive lives have high parity (and were therefore probably of normal weight in early adulthood) are more likely to experience weight gain across adulthood and be overweight or obese by middle-age than women who have no or fewer children.[208] If this is the case, while the group of women who are obese in early adulthood will consist mainly of women who are sub- or infertile, the group of women who are obese in later adulthood will consist not only of these women (given weight tracks across adult life) but also women of high parity. If women with higher parity are at increased risk of hysterectomy, investigated in the next chapter, and BMI and parity are associated in the NSHD in the way described, this would explain the different shapes of association between BMI at different ages across adulthood and hysterectomy rates found. This will be investigated in chapter 7 once the reproductive characteristics associated with hysterectomy have been identified especially as other factors such as age at menarche could also be important.

5.6.4 Limitations

No differences in association by reason for hysterectomy were found in these analyses. This could be because weight is influencing subsequent hysterectomy on a pathway not directly associated with medical need for hysterectomy. Another possibility is that the analyses do not have sufficient power to detect the differences which exist. The potential lack of power in many of the analyses is a limitation of the data which exists because: at later ages of BMI measurement most women who have had a hysterectomy are excluded, because their hysterectomy occurred at an earlier age; and at earlier ages of BMI measurement there was little variation in BMI and very few women were overweight or obese in adolescence or early adulthood in the NSHD. This problem is obviously greatest in the analyses by reason for hysterectomy when the women are split into even smaller groups.

Very few women were overweight or obese in early adulthood in the NSHD. This may limit the applicability of these findings to younger cohorts of women who as part of a period effect have higher prevalence of overweight and obesity from younger ages than the women in the NSHD. As overweight and obesity were much more rare amongst the women in the NSHD in early adulthood this may mean that differences between those women who were obese or overweight in early adulthood and other women of lower BMI are greater in the NSHD than in younger cohorts with variation in BMI determined by different factors in different birth cohorts.

Another potential limitation is that it was difficult to compare the effects of BMI at different ages on subsequent hysterectomy rates because of differences in N and the age range of included hysterectomies in analyses of BMI at different ages (e.g. in analyses of

BMI at age 26 years the association with hysterectomies performed between ages 27 and 57 years is tested whereas in analyses of BMI at age 53 years the association with hysterectomy performed between ages 54 and 57 years is tested). An attempt to overcome this was made by running a time-updated analysis but this considered BMI only in the time period immediately prior to hysterectomy and was not able to take into consideration BMI trajectories across life.

Although weight and height were measured by trained professionals at most data collection points across life, at ages 20 and 26 years this information was self-reported. There is some evidence that levels of overweight and obesity were underestimated at these ages in the NSHD as a result.[235] If this misclassification of weight was differential by hysterectomy status it is possible that an n-shaped relationship between BMI at ages 20 and 26 years and subsequent hysterectomy rates could have been found even though the real association is positive and linear. However, as the measures of weight at ages 20 and 26 years were taken before hysterectomies occurred such misclassification seems very unlikely and similar n-shaped associations were found between other measures of BMI, which were recorded by trained professionals, and hysterectomy.

BMI was selected as the measure of adiposity to be used in these analyses and enabled study of associations at time points across life as weight and height, the two measures required to calculate BMI, had been recorded regularly from infancy onwards in the NSHD. As BMI was used as a measure of weight adjusted for height, Pearson's correlation coefficients of the association between weight and BMI and, height and BMI at each age were calculated to check that weight and BMI but not height and BMI were correlated. These showed that BMI was highly correlated with weight and not with height at all ages except at age 2 years (results not shown) and even at this age the correlation between BMI and weight was greater than the correlation between BMI and height suggesting that it was appropriate to use BMI as a measure of adiposity in these analyses. However, the limitations of using BMI need to be assessed. One problem is that BMI does not distinguish between fat and lean mass[200;201;230] and so for a given BMI there is a large range of body fat percentages possible. Further, for a given BMI, body fat percentage increases with age[201;230] and in childhood and adolescence BMI changes with linear growth and puberty[200] leading to debates about the acceptability of using BMI especially at the extremes of age. However, despite these limitations it is widely acknowledged that BMI is the best proxy measure of overall adiposity from infancy to later adulthood (i.e. the time period covered in this study) capturing satisfactorily most of the relevant variation in overall levels of adiposity[200;201;230;244] and changes in adiposity over time[245] suggesting that it was an appropriate measure to use in these analyses. What BMI cannot capture is the distribution of fat mass across different anatomical sites of the body. Differences in fat distribution may be important as fat deposited at the abdomen tends to be more metabolically active than fat at peripheral locations.[200;230] Specific distributions of body fat, especially central deposits of adipose tissue, have been found to be more important in influencing the development of many chronic diseases than overall levels of adiposity[246;247] with some evidence of similar effects for a number of gynaecological outcomes.[248-251] However, as measures of fat distribution, more specifically of central adiposity (i.e. waist circumference and waist:hip ratio) have not been measured across life in the NSHD, only at ages 43 and 53 years, these effects cannot be properly studied using data from the NSHD, especially as such measures are hard to collect retrospectively. When the effect of waist:hip ratio and waist circumference at ages 43 and 53 years on subsequent hysterectomy rates was examined (results not shown) there were no important differences when compared to the results using BMI.

5.6.5 Strengths

As alluded to earlier in the discussion this study has a number of benefits compared to previous studies. Firstly weight and height were measured prospectively at a number of time points across life rather than only at one or two times, allowing a full examination of the differences in weight trajectories of women across life by subsequent hysterectomy status. Further, these measures are more likely to be valid than measures used in other studies as they were taken at all ages, except 20 and 26 years, by trained health professionals using a standardised protocol rather than by self-report. As the timings of hysterectomy are known a clear temporal relationship between weight and hysterectomy could be established, which was a major limitation in most previous studies. With information on reasons for hysterectomy it has also been possible to explore the associations between BMI and hysterectomy by reason which previous studies had not done.

The original cohort was selected to be nationally representative whereby the results from these analyses may be more generalisable than results from other studies. Although selective loss to follow-up could have introduced bias and reduced the generalisability of findings comparisons of those women included in analyses with those women not included (results not shown) found no significant differences between the two groups in mean BMI at any age.

5.6.6 Conclusions

These analyses have demonstrated that there was an association between BMI across adulthood and subsequent hysterectomy rates in the NSHD and that this association was complex. There was however, no association between BMI in childhood and hysterectomy. There are a number of possible explanations of these associations but which are most likely to be acting is not yet clear. How BMI in adulthood acts to influence hysterectomy risk will be investigated further in chapter 7, once the associations between reproductive characteristics, some of which are associated with BMI, and hysterectomy have been examined in the next chapter. This will allow more adequate conclusions to be drawn and the most likely implications of these findings to be identified.

Figure 5.1: Mean BMI by subsequent hysterectomy status in the NSHD (N=1,790)

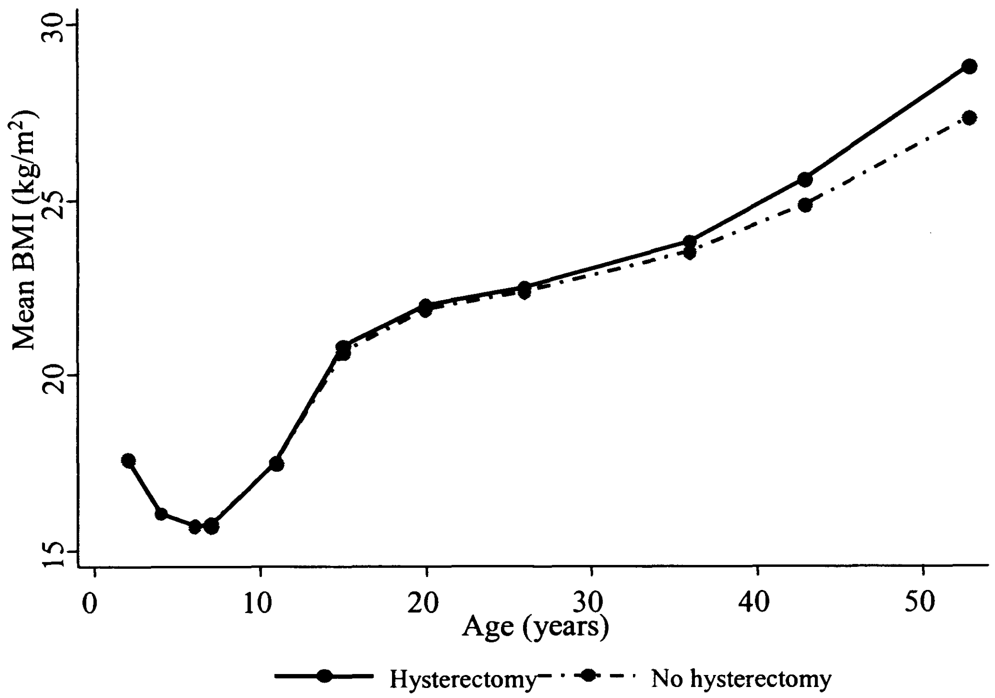


Figure 5.2: The unadjusted relationship between BMI at age 26 years and subsequent hysterectomy rates in the NSHD (N=1,534, number of hysterectomies=339)

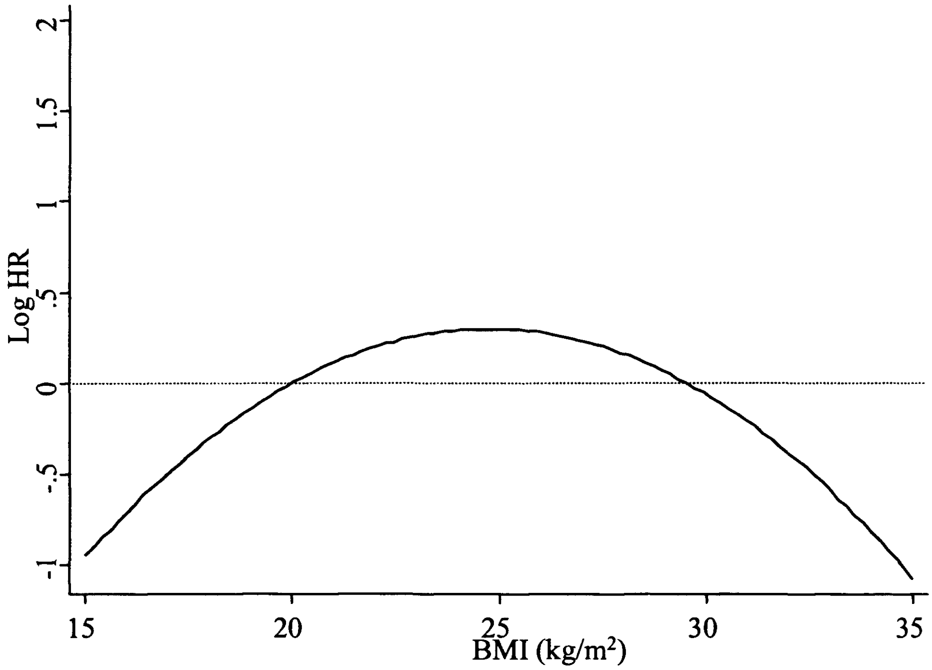


Figure 5.3: The unadjusted relationship between BMI at age 36 years and subsequent hysterectomy rates in the NSHD (N=1,510, number of hysterectomies=306)

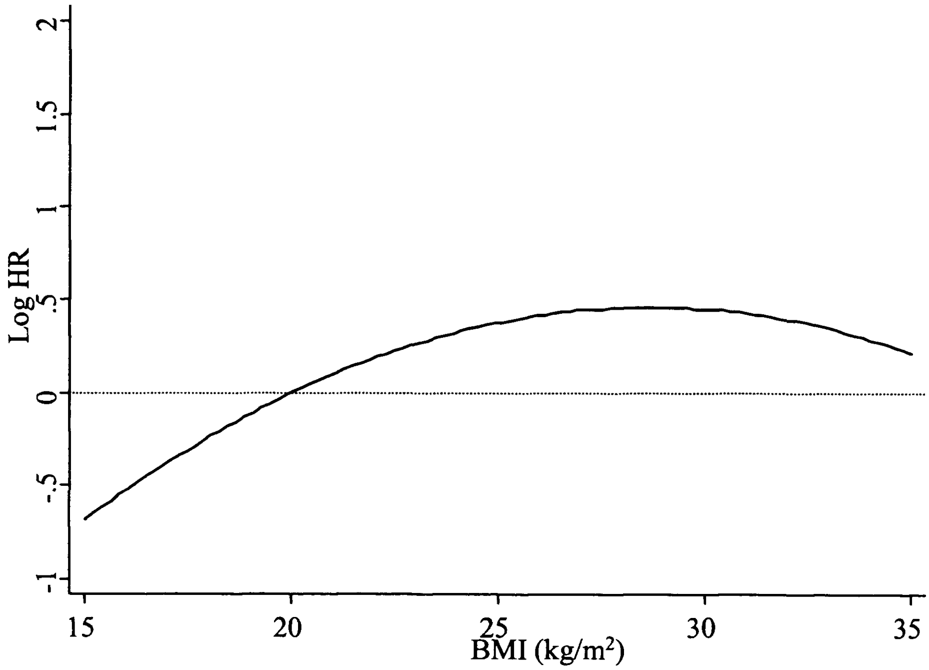


Figure 5.4: The unadjusted relationship between BMI at age 43 years and subsequent hysterectomy rates in the NSHD (N=1,439, number of hysterectomies=194)

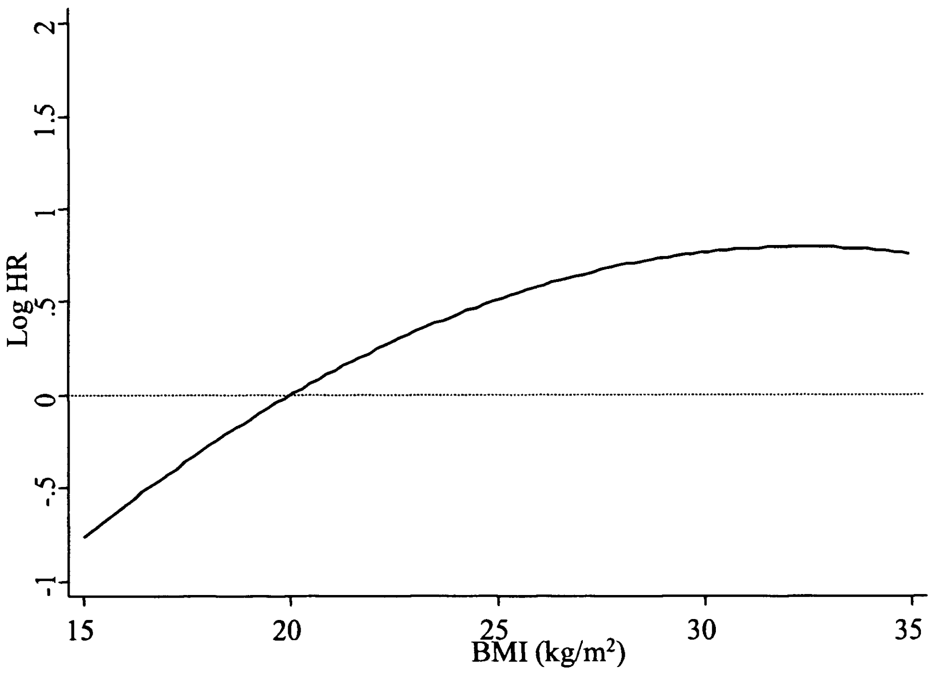


Figure 5.5: The unadjusted relationship between BMI at age 53 years and subsequent hysterectomy rates in the NSHD (N=1,170, number of hysterectomies=19)

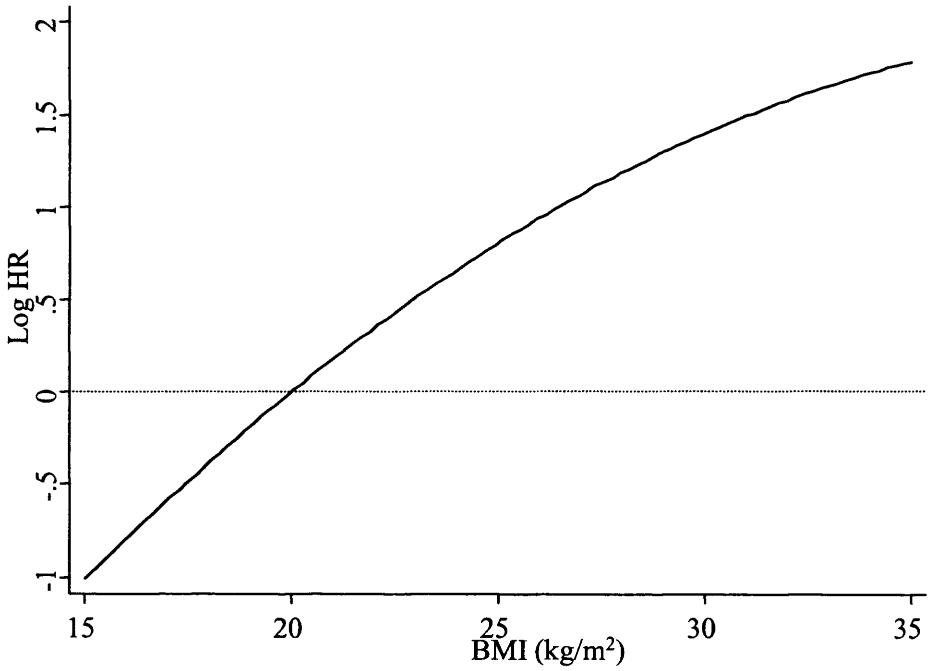


Figure 5.6: Possible pathways between BMI and subsequent hysterectomy

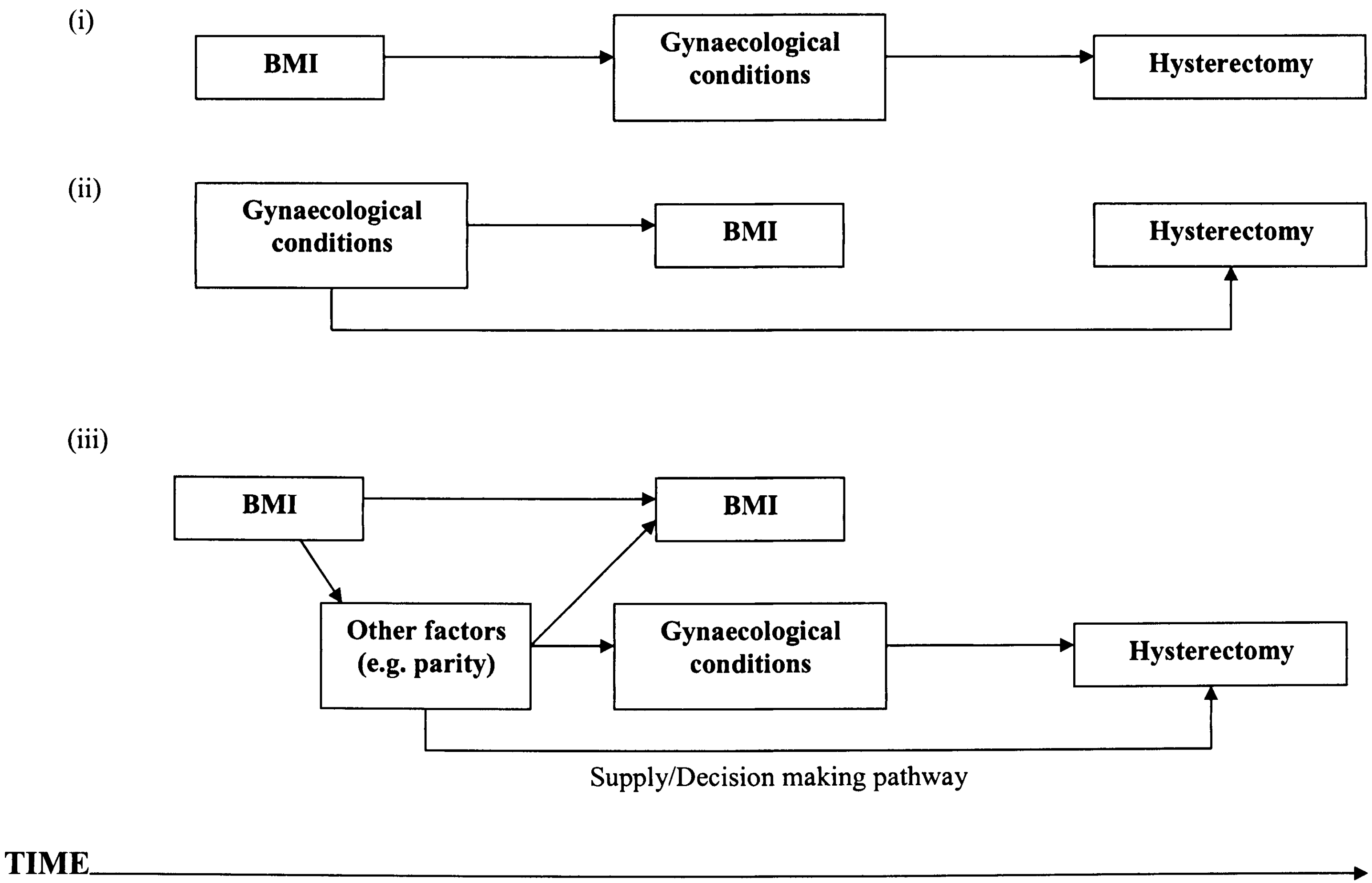


Table 5.1: Unadjusted survival analyses of the associations between BMI in childhood and adolescence and subsequent hysterectomy rates in the NSHD

BMI (kg/m^2) in:	Cut-off (kg/m^2)	N (%) [No. of hysterectomies]	Hysterectomy rate per 1000 women years (95% CI)	Hazard Ratio for hysterectomy (95% CI)	p-value
1948 (Age 2 years) (N=1352)					
Underweight /Normal	< 18.02	861 (63.68) [190]	5.45 (4.73, 6.28)	1.00	0.86*
Overweight	18.02 – 19.81	298 (22.04) [71]	5.84 (4.63, 7.37)	1.06 (0.81, 1.40)	0.59**
Obese	> 19.81	193 (14.28) [46]	5.87 (4.39, 7.83)	1.07 (0.78, 1.48)	
per 1 unit increase in BMI	-	1352 (100) [307]		1.00 (0.95, 1.04)	0.89*
1950 (Age 4 years) (N=1509)					
Underweight /Normal	< 17.28	1201 (79.59) [266]	5.46 (4.84, 6.16)	1.00	0.21*
Overweight	17.28 -19.15	242 (16.04) [61]	6.27 (4.88, 8.06)	1.16 (0.88, 1.54)	0.82**
Obese	> 19.15	66 (4.37) [10]	3.71 (2.00, 6.89)	0.67 (0.36, 1.26)	
per 1 unit increase in BMI	-	1509 (100) [337]		1.00 (0.94, 1.07)	0.91*
1952 (Age 6 years) (N=1427)					
Underweight /Normal	< 17.34	1256 (88.02) [280]	5.50 (4.89, 6.18)	1.00	0.80*
Overweight	17.34 – 19.65	154 (10.79) [38]	6.12 (4.46, 8.42)	1.12 (0.80, 1.57)	0.54**
Obese	> 19.65	17 (1.19) [4]	5.83 (2.19, 15.54)	1.07 (0.40, 2.88)	
per 1 unit increase in BMI	-	1427 (100) [322]		1.00 (0.92, 1.08)	0.96*
1953 (Age 7 years) (N=1482)					
Underweight /Normal	< 17.75	1348 (90.96) [301]	5.51 (4.92, 6.17)	1.00	0.78*
Overweight	17.75 – 20.51	118 (7.96) [23]	4.78 (3.18, 7.19)	0.87 (0.57, 1.33)	0.51**
Obese	> 20.51	16 (1.08) [3]	4.69 (1.51, 14.53)	0.87 (0.28, 2.70)	
per 1 unit increase in BMI	-	1482 (100) [327]		0.99 (0.92, 1.06)	0.81*
1957 (Age 11 years) (N=1470)					
Underweight /Normal	< 20.74	1320 (89.80) [282]	5.24 (4.67, 5.89)	1.00	0.07*
Overweight	20.74 – 25.42	128 (8.71) [30]	5.78 (4.04, 8.27)	1.11 (0.76, 1.62)	
Obese	> 25.42	22 (1.50) [1]	1.07 (0.15, 7.59)	0.20 (0.03, 1.39)	
per 1 unit increase in BMI†	-	1470 (100) [313]		0.96 (0.90, 1.02)	0.01*
per 1 unit increase in BMI^2				0.98 (0.97, 0.99)	0.007♦
1961 (Age 15 years) (N=1336)					
Underweight /Normal	< 23.94	1182 (88.47) [249]	5.16 (4.56, 5.84)	1.00	0.15*
Overweight	23.94 – 29.11	133 (9.96) [35]	6.59 (4.73, 9.17)	1.30 (0.91, 1.85)	
Obese	> 29.11	21 (1.57) [2]	2.31 (0.58, 9.22)	0.44 (0.11, 1.78)	
per 1 unit increase in BMI†	-	1336 (100) [286]		1.08 (1.02, 1.14)	0.02*
per 1 unit increase in BMI^2				0.99 (0.98, 1.00)	0.03♦

† significant deviation from linearity so BMI centred at 20 and a quadratic term included in the survival model $\log HR = \beta_1 BMI + \beta_2 BMI^2$

* p-value from likelihood ratio test ** p-value from test for trend (not shown if there was evidence of deviation from linearity) ♦ p-value from Wald test of quadratic term

Table 5.2: Unadjusted survival analyses of the associations between BMI in adulthood and subsequent hysterectomy rates in the NSHD

BMI (kg/m^2) in:	Cut-off (kg/m^2)	N (%) [No. of hysterectomies]	Hysterectomy rate per 1000 women years (95% CI)	Hazard Ratio for hysterectomy (95% CI)	p - value
1966 (Age 20 years) (N=1427)					
Underweight	< 20	381 (26.70) [76]	4.86 (3.89, 6.09)	0.83 (0.64, 1.08)	
Normal	20 – 25	888 (62.23) [210]	5.81 (5.08, 6.65)	1.00	0.47*
Overweight	25.1 – 30	130 (9.11) [30]	5.75 (4.02, 8.23)	1.01 (0.69, 1.48)	
Obese	> 30	28 (1.96) [5]	4.33 (1.80, 10.41)	0.74 (0.30, 1.78)	
per 1 unit increase in BMI†	-	1427 (100) [321]		1.09 (1.02, 1.18)	0.02*
per 1 unit increase in BMI^2				0.99 (0.98, 1.00)	0.03♦
1972 (Age 26 years) (N=1534)					
Underweight	< 20	312 (20.34) [50]	3.89 (2.95, 5.14)	0.65 (0.48, 0.88)	
Normal	20 – 25	968 (63.10) [231]	5.88 (5.17, 6.68)	1.00	0.006*
Overweight	25.1 – 30	211 (13.75) [53]	6.26 (4.78, 8.19)	1.08 (0.80, 1.45)	
Obese	> 30	43 (2.80) [5]	2.83 (1.18, 6.80)	0.47 (0.19, 1.15)	
per 1 unit increase in BMI†	-	1534 (100) [339]		1.13 (1.05, 1.22)	0.0008*
per 1 unit increase in BMI^2				0.99 (0.98, 1.00)	0.003♦
1982 (Age 36 years) (N=1510)					
Underweight	< 20	193 (12.78) [32]	4.00 (2.83, 5.65)	0.85 (0.59, 1.24)	
Normal	20 – 25	933 (61.79) [181]	4.68 (4.05, 5.41)	1.00	0.006*
Overweight	25.1 – 30	281 (18.61) [77]	6.82 (5.45, 8.52)	1.52 (1.16, 1.98)	
Obese	> 30	103 (6.82) [16]	3.76 (2.30, 6.13)	0.80 (0.48, 1.33)	
per 1 unit increase in BMI†	-	1510 (100) [306]		1.11 (1.04, 1.19)	0.005*
per 1 unit increase in BMI^2				0.99 (0.99, 1.00)	0.009♦
1989 (Age 43 years) (N=1439)					
Underweight	< 20	106 (7.37) [8]	1.36 (0.61, 3.02)	0.42 (0.18, 0.96)	
Normal	20 – 25	799 (55.52) [104]	3.10 (2.56, 3.76)	1.00	0.03*
Overweight	25.1 – 30	361 (25.09) [55]	3.60 (2.76, 4.69)	1.19 (0.86, 1.65)	
Obese	> 30	173 (12.02) [27]	3.84 (2.65, 5.56)	1.28 (0.84, 1.94)	
per 1 unit increase in BMI†	-	1439 (100) [194]		1.14 (1.05, 1.23)	0.001*
per 1 unit increase in BMI^2				0.99 (0.99, 1.00)	0.01♦
1999 (Age 53 years) (N=1170)					
Underweight	< 20	35 (2.99) [0]	-	no hysterectomies	
Normal	20 – 25	431 (36.84) [5]	0.26 (0.11, 0.63)	1.00	0.24*
Overweight	25.1 – 30	413 (35.30) [6]	0.33 (0.15, 0.74)	1.27 (0.39, 4.17)	0.07**
Obese	> 30	291 (24.87) [8]	0.63 (0.31, 1.26)	2.56 (0.84, 7.82)	
per 1 unit increase in BMI	-	1170 (100) [19]		1.07 (1.00, 1.13)	0.04*

† significant deviation from linearity so BMI centred at 20 and a quadratic term included in the survival model $\log HR = \beta_1 BMI + \beta_2 BMI^2$

* p-value from likelihood ratio test ** p-value from test for trend (not shown if there was evidence of deviation from linearity) ♦ p-value from Wald test of quadratic term

Table 5.3: Survival analyses of the association between BMI at 53 years and subsequent hysterectomy rates adjusted for BMI at 43 and 36 years in the NSHD

Variables included in the model	**N (no. of hysterectomies)**	**Unadjusted Hazard Ratio for hysterectomy (95% CI)**	**Hazard Ratio for hysterectomy (95% CI) adjusted for other variable**
BMI at 53 years	1103 (18)	1.07 (1.01, 1.14)	1.09 (0.92, 1.28)
p-value		*0.03*	*0.32*
BMI at 43 years		1.07 (1.00, 1.15)	0.98 (0.81, 1.18)
p-value		*0.06*	*0.85*
BMI at 53 years	1050 (15)	1.08 (1.01, 1.16)	1.21 (1.05, 1.39)
p-value		*0.02*	*0.008*
BMI at 36 years		1.05 (0.93, 1.17)	0.82 (0.66, 1.03)
p-value		*0.43*	*0.09*

Table 5.4: Unadjusted survival analyses of the associations between BMI in childhood and subsequent hysterectomy rates by reason for hysterectomy in the NSHD

	Hazard Ratio for hysterectomy for specified reason (95% CI) [No. of hysterectomies]					
BMI (kg/m^2) in:	**Fibroids**	**Menstrual disorders**	**Prolapse**	**Cancer**	**Other**	**Unknown**
1948 (Age 2 years) (N=1352)	[N=93]	[N=86]	[N=31]	[N=19]	[N=49]	[N=29]
per 1 unit increase in BMI	0.99 (0.91,1.08)	1.08 (1.00,1.16)	0.93 (0.79,1.09)	0.89 (0.72,1.11)	0.94 (0.83,1.07)	0.97 (0.83,1.14)
p-value	*0.84*	*0.07*	*0.37*	*0.28*	*0.33*	*0.73*
1950 (Age 4 years) (N=1509)	[N=101]	[N=98]	[N=37]	[N=22]	[N=52]	[N=27]
per 1 unit increase in BMI	1.02 (0.91,1.15)	1.05 (0.94,1.18)	0.93 (0.77,1.14)	1.05 (0.82,1.35)	0.93 (0.78,1.10)	0.96 (0.76,1.21)
p-value	*0.69*	*0.40*	*0.51*	*0.68*	*0.38*	*0.70*
1952 (Age 6 years) (N=1427)	[N=104]	[N=87]	[N=35]	[N=22]	[N=49]	[N=25]
per 1 unit increase in BMI	0.98 (0.85,1.12)	1.07 (0.93,1.23)	1.03 (0.82,1.29)	1.03 (0.77,1.38)	0.82 (0.66,1.01)	1.10 (0.85,1.43)
p-value	*0.75*	*0.35*	*0.80*	*0.83*	*0.06*	*0.47*
1953 (Age 7 years) (N=1482)	[N=104]	[N=93]	[N=30]	[N=25]	[N=50]	[N=25]
per 1 unit increase in BMI	1.02 (0.90,1.15)	1.00 (0.88,1.14)	0.98 (0.77,1.23)	0.98 (0.76,1.26)	0.94 (0.78,1.13)	0.98 (0.76,1.27)
p-value	*0.76*	*0.99*	*0.84*	*0.85*	*0.49*	*0.90*

Table 5.5: Unadjusted survival analyses of the associations between BMI in adolescence and early adulthood and subsequent hysterectomy rates by reason for hysterectomy in the NSHD

BMI (kg/m^2) in:	Hazard Ratio for hysterectomy for specified reason (95% CI) [No. of hysterectomies]					
	Fibroids	Menstrual disorders	Prolapse	Cancer	Other	Unknown
1957 (Age 11 years) (N=1470)	[N=102]	[N=87]	[N=32]	[N=19]	[N=49]	[N=24]
per 1 unit increase in BMI	0.92 (0.81, 1.04)	0.99 (0.89, 1.10)	0.91 (0.72, 1.15)	1.00 (0.83, 1.21)	0.88 (0.72, 1.08)	1.05 (0.90, 1.23)
per 1 unit increase in BMI^2	0.98 (0.95, 1.00)	0.98 (0.96, 1.00)	0.97 (0.93, 1.02)	0.99 (0.95, 1.04)	0.98 (0.94, 1.02)	0.99 (0.96, 1.03)
*p-value**	*0.11*	*0.17*	*0.46*	*0.94*	*0.29*	*0.60*
*p-value***	*0.08*	*0.11*	*0.31*	*0.77*	*0.25*	*0.58*
1961 (Age 15 years) (N=1336)	[N=90]	[N=83]	[N=27]	[N=18]	[N=46]	[N=22]
per 1 unit increase in BMI	1.08 (0.96, 1.20)	1.08 (0.98, 1.20)	1.15 (0.95, 1.41)	1.02 (0.82, 1.27)	1.04 (0.90, 1.20)	1.20 (0.95, 1.50)
per 1 unit increase in BMI^2	0.97 (0.94, 1.00)	1.00 (0.99, 1.01)	0.98 (0.95, 1.02)	0.99 (0.96, 1.03)	0.98 (0.95, 1.01)	0.98 (0.95, 1.02)
*p-value**	*0.02*	*0.17*	*0.33*	*0.93*	*0.38*	*0.25*
*p-value***	*0.03*	*0.64*	*0.34*	*0.73*	*0.26*	*0.34*
1966 (Age 20 years) (N=1427)	[N=107]	[N=87]	[N=32]	[N=21]	[N=50]	[N=24]
per 1 unit increase in BMI	1.09 (0.96, 1.25)	1.17 (1.02, 1.35)	0.94 (0.79, 1.13)	0.96 (0.74, 1.25)	1.19 (0.98, 1.45)	1.23 (0.87, 1.74)
per 1 unit increase in BMI^2	0.98 (0.96, 1.00)	0.99 (0.97, 1.00)	1.00 (0.99, 1.02)	1.00 (0.96, 1.03)	0.98 (0.96, 1.01)	0.96 (0.89, 1.02)
*p-value**	*0.15*	*0.04*	*0.81*	*0.72*	*0.16*	*0.24*
*p-value***	*0.12*	*0.15*	*0.73*	*0.81*	*0.22*	*0.19*
1972 (Age 26 years) (N=1534)	[N=108]	[N=96]	[N=35]	[N=20]	[N=52]	[N=28]
per 1 unit increase in BMI	1.27 (1.07, 1.51)	1.16 (1.01, 1.33)	1.32 (0.96, 1.81)	1.08 (0.84, 1.40)	1.08 (0.92, 1.26)	0.99 (0.82, 1.21)
per 1 unit increase in BMI^2	0.96 (0.94, 0.99)	0.99 (0.98, 1.00)	0.96 (0.91, 1.01)	1.00 (0.97, 1.02)	0.99 (0.98, 1.01)	1.00 (0.98, 1.01)
*p-value**	*0.001*	*0.07*	*0.07*	*0.81*	*0.64*	*0.98*
*p-value***	*0.006*	*0.11*	*0.09*	*0.67*	*0.49*	*0.95*

*p-value from likelihood ratio test

** p-value from Wald test of quadratic term

Table 5.6: Unadjusted survival analyses of the associations between BMI in adulthood and subsequent hysterectomy rates by reason for hysterectomy in the NSHD

	Hazard Ratio for hysterectomy for specified reason (95% CI) [No. of hysterectomies]					
BMI (kg/m^2) in:	**Fibroids**	**Menstrual disorders**	**Prolapse**	**Cancer**	**Other**	**Unknown**
1982 (Age 36 years) (N=1510)	[N=107]	[N=91]	[N=30]	[N=18]	[N=39]	[N=21]
per 1 unit increase in BMI	1.18 (1.04, 1.34)	1.12 (0.99, 1.28)	1.01 (0.84, 1.21)	1.18 (0.92, 1.51)	1.05 (0.89, 1.23)	1.20 (0.86, 1.69)
per 1 unit increase in BMI^2	0.99 (0.98, 1.00)	0.99 (0.98, 1.00)	1.00 (0.99, 1.01)	1.00 (0.98, 1.01)	1.00 (0.99, 1.01)	0.98 (0.95, 1.01)
*p-value**	*0.02*	*0.15*	*0.94*	*0.20*	*0.70*	*0.35*
*p-value***	*0.03*	*0.10*	*0.94*	*0.49*	*0.82*	*0.27*
1989 (Age 43 years) (N=1439)	[N=73]	[N=42]	[N=27]	[N=9]	[N=24]	[N=19]
per 1 unit increase in BMI	1.16 (1.01, 1.33)	1.56 (1.15, 2.13)	1.03 (0.86, 1.23)	1.55 (1.08, 2.24)	1.03 (0.87, 1.22)	1.16 (0.89, 1.52)
per 1 unit increase in BMI^2	0.99 (0.98, 1.00)	0.97 (0.95, 0.99)	1.00 (0.99, 1.01)	0.99 (0.97, 1.00)	1.00 (0.99, 1.01)	0.99 (0.98, 1.01)
*p-value**	*0.06*	*0.002*	*0.94*	*0.002*	*0.61*	*0.47*
*p-value***	*0.09*	*0.01*	*0.84*	*0.11*	*0.93*	*0.38*
1999 (Age 53 years) (N=1170)	[N=2]	[N=2]	[N=7]	[N=3]	[N=3]	[N=2]
per 1 unit increase in BMI	0.95 (0.69,1.29)	1.09 (0.92,1.29)	1.06 (0.95,1.18)	1.16 (1.05,1.29)	0.77 (0.52,1.13)	1.11 (0.96,1.29)
*p-value**	*0.71*	*0.41*	*0.32*	*0.02*	*0.11*	*0.24*

*p-value from likelihood ratio test

** p-value from Wald test of quadratic term

Chapter 6: Reproductive characteristics and hysterectomy

Main objective: To investigate whether a range of reproductive characteristics are associated with hysterectomy risk.

6.1 Introduction

In the previous two chapters, the associations between personal attributes (i.e. SEP and BMI) which can vary over time and hysterectomy were examined. This chapter differs in that the majority of factors it considers are events and, these occur only once (e.g. menarche) or, if they occur at all, a limited number of times (e.g. childbirth, miscarriage) across life. Age at menarche, timing of first birth, parity, experience of stillbirth or miscarriage, infertility, subfertility and oral contraceptive (OC) use are the characteristics examined.

Hysterectomy by its nature ends a woman's reproductive life if it is not predated by natural menopause. The methodological issues which limit previous studies and which need to be considered in this chapter are therefore different from those in the previous chapter, as reproductive events, even if collected retrospectively, cannot occur after hysterectomy.

Reproductive characteristics could act on social and/or biological pathways to influence hysterectomy risk and, as mentioned in chapter 3 reproductive characteristics are one set of plausible mediating factors between SEP, BMI and hysterectomy. It is also plausible that the association between some reproductive characteristics and hysterectomy could be mediated by BMI or SEP.

There are a heterogeneous range of pathways along which the reproductive characteristics examined in this chapter could influence risk of hysterectomy. Reproductive characteristics are associated with lifetime exposure to oestrogen (i.e. age at menarche,[252;253] OC use,[254] parity/nulliparity[252;254]), damage to gynaecological organs and the pelvic structure (i.e. childbirth[127;255]), BMI (i.e. age at menarche,[256] parity[208;236]) and exposure to sexually transmitted diseases (i.e. age at first birth through its association with age at initiation of sexual activity,[122] OC use[257]) all of which are factors associated with the development of gynaecological conditions and hence medical need for hysterectomy. Other reproductive characteristics such as infertility and subfertility do not influence but instead indicate underlying, existing gynaecological morbidity and so indicate medical need for hysterectomy.

In addition to associations with factors that influence medical need for hysterectomy (i.e. biological pathways), reproductive characteristics could also influence risk of hysterectomy through their influence on decision making processes. Considerations women have to make such as desire to preserve fertility or conversely, desire to prevent risk of further pregnancies are associated with reproductive characteristics as are other factors which influence women's choice and health-seeking behaviour such as tolerance of pain and morbidity. Supply factors such as the likelihood of a doctor recommending a hysterectomy could also be associated with reproductive characteristics.

Some characteristics such as age at menarche, parity and OC use, if they are associated with hysterectomy, could all be acting on the same pathway, for example through their influence on oestrogen exposure. It is also plausible that they each operate on different pathways. Further, the same reproductive characteristic could be operating on multiple pathways.

6.2 Literature review

Twenty two studies[1;119;120;122;123;125-130;132;137;140;141;143;144;151;153;165;167;171] have examined the association between one or more reproductive characteristic and hysterectomy (for summarised details of studies see appendix 6). However, most of these studies have considered only one or two reproductive characteristics and have not drawn together the evidence on the different characteristics despite the fact that these may be operating on the same pathways or, that some reproductive characteristics could be mediating or confounding the association found between other reproductive characteristics and hysterectomy.

6.2.1 Age at menarche and age at first birth

Due to the similarity in the direction of associations found between age at menarche, age at first birth and risk of hysterectomy these two reproductive characteristics are considered in this review together.

Six studies[120;125;129;132;151;167] have assessed the association between age at menarche and hysterectomy and, seven[122;125;129;137;144;151;165] have assessed the association between age at first birth and hysterectomy. Most of these studies found inverse associations with women who had an earlier age at menarche[120;125;129;132;167] and who had an earlier age at first birth[122;125;129;137;144;151;165] experiencing increased risk of hysterectomy. The one exception was a study in Ireland[151] which found no association between either characteristic and hysterectomy although, this study only compared mean ages at menarche and first birth by hysterectomy status, a method which would not necessarily detect a difference in the distributions of ages at menarche or first birth between the hysterectomised and non-hysterectomised group even if they existed.

That the finding of inverse associations between age at menarche, age at first birth and hysterectomy is consistent across studies conducted at different times, in different countries using different methodology suggests that there could be real associations between these two reproductive characteristics and hysterectomy. However, the studies to date which have assessed this association have all used self-reported retrospective measures, a potential limitation especially for age at menarche.[258] Further, few studies have controlled for potentially confounding factors, none have analysed hysterectomies for different reasons separately or considered the pathways on which these characteristics may be operating which is especially important for age at first birth given associations with hysterectomy could be found because of its strong correlation with other reproductive characteristics such as parity (women who start having children at a younger age have a longer period of time in which to have children) and socioeconomic factors. No study has considered the possibility that the association between one of these characteristics and hysterectomy could be explained by the other characteristic given they show a similar pattern of association with hysterectomy and have sometimes been found to be positively associated with each other.[259] In the NSHD, however, age at menarche and age at first birth were not associated,[260] and so are unlikely to confound each other

6.2.2 Parity

Most studies which have assessed the association between at least one reproductive characteristic and hysterectomy have considered parity.[1;119;120;122;123;125-130;137;140;141;143;144;151;153;165;167;171] The association between parity and hysterectomy is less consistent across studies than the association between either age at menarche or first birth and hysterectomy. The majority of studies[1;119;125;127;129;137;140;141;143;151;153;165] found some evidence of a positive association between parity and hysterectomy with women who had more children experiencing greater risk of hysterectomy than women with fewer or no children. Three other studies,[122;128;167] while finding similarly that women with high parity had increased risk of hysterectomy, also found that women who were nulliparous had increased risk of hysterectomy compared to women with only one or a few children suggesting that the relationship may be non-linear. A further five studies[120;126;130;144;171] found no association and one found a negative association.[123]

There is no clear reason for the inconsistencies between studies with study design or country or time of study likely to explain some but not all of the differences found. Some of the inconsistencies could be explained by differences in the way parity was categorised in different analyses. For example, in one study[137] which found a positive, linear association between parity and hysterectomy, women who had no children were grouped with women who had one child and so any difference in effect of having had one child compared to having no children would not be detected and any effect specific to one of these groups would have been diluted. In four other studies which found positive associations[140;141;143;153] the categories ever pregnant vs. never pregnant and nulliparous vs. parous were used and so any difference between women with different numbers of children would not be detected and the greater risk of hysterectomy associated with having had many children, demonstrated in most studies, would drive the association seen hiding any more subtle differences. Other possible explanations for the inconsistencies include differences in the reasons for hysterectomy in different study populations, differences in the level of importance of supply factors in determining rates of hysterectomy in different populations and different reasons for nulliparity in different populations.

As more attention has been given to the association between parity and hysterectomy than any other reproductive characteristic there has also been a greater consideration of the role of potential confounders and effect modifiers. In a study of Danish women,[167] adjustment for a range of social and weight-related factors attenuated the effect of parity on hysterectomy. Unfortunately as many variables were entered into the same model it is difficult to identify which factors were explaining the association found in unadjusted analyses. In an American study,[122] the association between parity and hysterectomy attenuated after adjustment for age at first birth and, in an Australian study[128] the same association attenuated after adjustment for a range of factors. Evidence of effect modification was also found in some studies. Meilahn and colleagues,[125] found a positive association between parity and hysterectomy but only amongst black women. Santow and Bracher[127] found that although there was an increased risk of hysterectomy for all women after their third birth this risk was much greater if the third birth occurred before age 25.

In one study,[1] the association between parity and hysterectomy by reason was examined. Vessey and colleagues found a positive association between parity and hysterectomy overall in a UK population. A similar pattern of association was seen when considering hysterectomies for menstrual problems and prolapse with nulliparous women having lower rates of hysterectomy for these two reasons than women with children. Conversely, nulliparous women had higher rates of hysterectomy for fibroids than parous women. There was no significant association between parity and hysterectomy for cancer or endometriosis.

Previous studies provide justification for studying the association between parity and hysterectomy further. As well as having a number of limitations including inappropriate categorisation of parity there has also been little attempt to identify the pathways on which parity may be acting to influence hysterectomy risk or consider how other reproductive characteristics may interact with or explain the effect of parity. The previous studies also suggest factors which should be considered as potential confounders/mediators and highlight the need to consider hysterectomies by reason.

6.2.3 Miscarriages and infertility

Seven studies[119;122;127;128;130;137;167] have considered the effect of unsuccessful attempts to bear children on risk of hysterectomy by examining the effect of fetal loss (i.e. miscarriage, induced abortion or stillbirth) or infertility and subfertility.

Women who have experienced fetal loss have been found to have higher risk of hysterectomy in all studies which have examined this.[119;122;127;130;137;167] In one study[127] this association was only seen if women had experienced at least two losses before age 35. In another study[167] there was no association between fetal loss and prevalent hysterectomies as measured at baseline but there was an association with incident hysterectomies which occurred during follow-up. In an assessment of the association by reason for hysterectomy, Brett and colleagues[137] found that women who had suffered ≥ 3 miscarriages had higher risk of hysterectomy overall and for prolapse but lower risk of hysterectomy for fibroids than women who had reported 0 – 2 miscarriages.

Although these studies are considered together they are not all examining exactly the same predictor. While the majority of studies consider only miscarriages, other studies consider all fetal losses without defining this further and another study[167] groups all spontaneous and induced abortions together despite the likely differences between women having induced abortion and women whose abortion is spontaneous.

Only two studies[128;144] have assessed the effect of infertility or subfertility on risk of hysterectomy. The first of these[128] found an association between consulting a doctor because of problems conceiving and hysterectomy. The other study[144] assessed the association between the markers of subfertility, interval between menstrual cycles and episodes of amenorrhea, both of which were found to be associated with hysterectomy - women who had shorter intervals between menstrual periods and women who had less amenorrhic episodes had greater risk of hysterectomy than other women. The lack of research on this justifies the need for further study.

6.2.4 Oral contraceptive use

Seven studies[119;120;127;130;144;151;167] have assessed the association between OC use and hysterectomy. In over half of these[119;120;130;144] there was no association. In only one study[151] was there a clear positive association between length of OC use and hysterectomy. In the other two studies[127;167] long-term users (i.e. > 5 years) had reduced risk of hysterectomy and short-term users (i.e. 1 - 4 years) had increased risk[167] or no difference in risk[127] compared to never users.

The lack of consistency between studies could be attributable to a number of factors including differences in times and places of study. These factors are likely to be more influential in analyses of OC than in analyses of other reproductive characteristics because of the greater cultural influences over and, the different reasons for OC use (i.e. OC can be prescribed to control menstrual problems as well as being used as a contraceptive). It is also possible that OC use is less reliably reported than other reproductive characteristics and so subject to more errors and bias. Similar characteristics such as use of an intra-uterine device and tubal sterilisation show equally inconsistent results across studies.

6.2.5 General appraisal of published studies

6.2.5.1 Countries of study

Studies of the association between reproductive characteristics and hysterectomy have been conducted in a range of countries including Finland,[123] Australia,[127;128;132] New Zealand,[153] the Netherlands,[140] Sweden,[144] Italy[126;171] and Austria[165] although as for the study of other predictors of hysterectomy the majority have been done in the USA.[120;122;125;129;130;137;141;143] Only one study[1] has included British women and this considered only one reproductive characteristic, parity. Therefore, for the same reason as suggested in the previous chapter i.e. that there is wide variation in rates of hysterectomy between countries,[104] it would be informative to examine in detail whether relationships between a range of different reproductive characteristics across life and hysterectomy are evident in British women.

6.2.5.2 Definition of hysterectomy

As found when reviewing the literature for the previous two chapters there is no consistency in the definitions of hysterectomy used across different studies – the majority of studies include hysterectomies for all reasons, others include only hysterectomies performed for benign reasons[126;167] and others group women who have had only an oophorectomy with women who have had a hysterectomy.[125]

6.2.5.3 Measurement of reproductive characteristics

Most reproductive characteristics used in existing studies are self-reported retrospectively. It would be expected that this method of measurement would be less valid than prospective measurement for most reproductive characteristics. While it could be argued that some characteristics, such as parity, age at first birth, suffering from a miscarriage or experiencing fertility problems would be remembered accurately however long after the event they are asked about because of the significance of these in women's lives, there are also factors such as embarrassment and a perceived stigma attached to the latter two of these experiences which could detrimentally affect women's reporting of these characteristics. Further, a recent study using data from the NSHD[258] suggests that age at menarche is only moderately valid when recalled in adulthood and is subject to biases implying that the same may be true for other reproductive characteristics.

6.2.6 Summary of findings from the literature review

There is some evidence from existing studies that reproductive characteristics are associated with risk of hysterectomy but this is still far from conclusive with studies limited by many of the same general limitations found in the studies reviewed in the previous two chapters including: the wide age range of study populations; a reliance on self-reported retrospective data which has not been validated; and the use of unrepresentative populations. Further, the pathways on which all these characteristics act remain to be identified. The findings from existing studies are most consistent for age at menarche, age at first childbirth and fetal loss and least consistent for parity and OC use. For parity, the most widely studied characteristic, there is evidence that the association may be confounded or modified by other reproductive characteristics and demographic, social and weight-related factors. For other reproductive characteristics the effect of confounders and effect modifiers has not been so well considered and requires further attention. In the two studies[1;137] which have analysed hysterectomies separately by reason there is evidence that the association between parity, miscarriages and hysterectomy does differ by reason suggesting the need to investigate this further.

6.3 Specific objectives of the chapter

The specific objectives to be addressed in this chapter are:

i. to examine whether reproductive characteristics are associated with hysterectomy rates
ii. to examine whether the relationships between individual reproductive characteristics and hysterectomy rates are independent of the association between other reproductive characteristics and hysterectomy
iii. to examine whether the associations between reproductive characteristics and hysterectomy rates differ by reason for hysterectomy

6.4 Methods

6.4.1 Main outcome variable

Hysterectomy with or without oophorectomy

6.4.2 Main explanatory variables

Age at menarche, age at first birth, parity at age 30 years, experience of stillbirth or miscarriage, infertility, subfertility (length of time between birth of first and second child, irregular/infrequent menstrual cycles) and OC use.

6.4.3 Ascertainment of reproductive characteristics

The reproductive characteristics used in this chapter were all selected a priori because they are the main influences on or markers of lifetime reproductive function. Measurement of the selected characteristics occurred at various data collection points.

6.4.3.1 Age at menarche

Age at menarche was first recorded during medical examinations performed when cohort members were aged 11 years and then again at age 14 or 15 years. At these times school doctors established whether the female members of the cohort had started their periods and if so, the month and year of onset of the first period. If a cohort member had not reached menarche by the time of the interview at age 14/15 years this was recorded. At age 48 years, all female members of the cohort were again asked, in the 1994 'Women's Health in the Middle Years' questionnaire, for the age in years at which their periods started. The information from these data collections was combined to create a continuous age at menarche variable in years for use in these analyses. This was done using an order of preference with age at menarche reported in early life being used if it was available (n=1,294). For those women known not to have reached menarche by the time of the data collection at age 14/15 years and who reported an age at menarche greater than 13 at age 48 years (n=94), the age at menarche reported at age 48 years was used. Women recorded as not having reached menarche at age 14/15 years who then reported an age at menarche younger than 14 at age 48 years (n=10) were not included because the age available (i.e. that reported at age 48 years) was likely to be incorrect. In addition, women whose age at menarche was missing from the data collection in adolescence who reported an age at menarche at age 48 years (n=240) were not included because as referred to earlier, analyses using data from the NSHD[258] suggested that age at menarche recalled in adulthood was only moderately valid and could introduce bias.

As well as considering age at menarche as a continuous variable it was also categorised into four groups: ≤11; 12; 13; ≥14 years. This categorical variable had a slightly larger N as all women who were known not to have reached menarche by the time of the data collection in adolescence, including those women for whom a valid age of menarche was not reported at age 48 years or was reported to be less than 14 (n=50), were included in the upper category along with all women who had a known age at menarche recorded in adolescence.

6.4.3.2 Childbirth

Information on live births was ascertained at data collections across adulthood. In determining which measure of parity to use it was necessary to consider the fact that hysterectomy, if it occurs before menopause, ends reproductive life so could itself influence parity. To limit problems which may be related to this, parity achieved by age 30 years was used. This age was selected as most hysterectomies (i.e. 96%) occurred after this age and, it provided an accurate reflection of women's parity at the end of reproductive life given most women in the NSHD had their children early in life (only 8% (n=123) of parous women had their first child at an age > 30 years). Parity was considered as a continuous variable and also categorised into a binary variable (nulliparous vs. parous) and a categorical variable with 4 groups (0; 1; 2; ≥3 children). Age at first birth was considered as a continuous variable and also categorised into 4 groups: 15 – 20; 21 – 25; 26 – 30; ≥31 years.

6.4.3.3 Stillbirth/Miscarriage

A number of other reproductive measures were ascertained from women's responses to questions in the questionnaire self-completed during the home visit in 1989. In this questionnaire women were asked whether they had ever had a stillbirth or miscarriage and if so, how many of each. Using the information from the first of these questions a binary variable ever had a stillbirth or miscarriage (yes vs. no) was created. As it was thought that there could be some difference between women who experienced only one stillbirth or miscarriage and women who experienced multiple such events a second variable was created with the categories: Never had a stillbirth or miscarriage; Had one stillbirth or miscarriage; Had more than one stillbirth and/or miscarriage.

6.4.3.4 Infertility

Women were also asked in the 1989 questionnaire whether they had ever consulted a doctor or other professional about infertility and if so, whether the reason they could not have children was because of their own fertility, their partner's fertility, fertility problems for both or there was no fertility problem. From this information a binary variable ever consulted a doctor about infertility (yes vs. no) was created. A second variable incorporating the information on reason for infertility problems was also created with three categories: Never consulted a doctor or consulted a doctor but no problems found or problems due to partner's fertility; Consulted a doctor and problems due to own or both partners' fertility; Consulted a doctor reason for infertility not reported.

6.4.3.5 Subfertility

The reproductive characteristics parity, ever suffered a miscarriage and ever consulted a doctor about infertility were used by Kok and colleagues[261] as markers of subfertility. In addition to these variables, Kok and colleagues also considered irregular menstrual cycles and length of time between birth of first and second child greater than five years. In order to assess the effect of subfertility on risk of hysterectomy these two additional measures were also considered in these analyses. In the 1997 'Women's Health in the Middle Years' postal questionnaire women were asked whether they had ever had infrequent or irregular menstrual cycles. If they answered yes to this question they were asked how often this occurred (i.e. not at all; a little; a lot) in each of the different age-bands (adolescence; 20-29; 30-39; 40-49; since aged 50 years). As it was intended that irregular periods should be a marker of subfertility and not of problems associated with menarche as could be the case in adolescence or, with the onset of menopause as could be the case in women's 40s and 50s reports of irregular or infrequent menstrual cycles in only the age-bands 20-29 and 30-39 years were classified as a positive exposure and a variable with three categories (Did not have infrequent or irregular menstrual cycles in 20s and 30s; Had infrequent or irregular menstrual cycles in 20s and/or 30s a little; Had infrequent or irregular menstrual cycles in 20s and/or 30s a lot) was created. To calculate the length of time between the birth of the first and second child the age at first childbirth was subtracted from the age at second childbirth for those women who had ≥ 2 children and this was then categorised to create a binary variable: 0-5 years vs. > 5 years.

6.4.3.6 Oral contraceptive use

Information on OC use was taken from the 1989 questionnaire and the 1997 'Women's Health in the Middle Years' questionnaire. In both questionnaires women were asked whether they had ever taken the OC pill. From this information a binary variable ever taken OCs (yes vs. no) was created with women who reported having used OCs in response to either questionnaire coded as yes. In 1989 women were also asked their age at first taking OCs and the number of years during which they had taken OCs including all episodes of use. This information was used to create the variables age at first use (categorised as: Never used; 15-20; 21-25; 26-30; >30 years; Used OCs but age at first use unknown) and duration of use (categorised as: Never used; 1-5; 6-10; 11-15; 16-30 years; Used but for unknown duration).

6.4.4 Analyses

6.4.4.1 Analyses to address objective (i) – unadjusted associations

Cox's proportional hazards models were used to test the unadjusted association between each reproductive characteristic and hysterectomy. In the first set of models all characteristics were entered as categorical variables. Where appropriate i.e. for measures such as age at menarche, age at first birth, parity, age at first OC use and duration of OC use which had been categorised but were also available for analysis as continuous variables, tests of deviation from linearity were performed. Where there was no evidence of deviation from linearity tests for trend were performed and these reproductive characteristics were entered individually into a second set of models as continuous variables.

6.4.4.2 Analyses to address objective (ii) – adjusted associations

The association between each reproductive characteristic and every other was individually tested using chi-squared tests or if both variables were continuous by Pearson's correlation coefficients.

To avoid testing associations which were unlikely to produce significant results other than by chance and to limit the overall number of statistical tests performed reproductive characteristics which were not associated with hysterectomy rates in unadjusted models performed to address objective (i) were not considered in multivariable models.

Based on a priori hypotheses that parity and age at first birth could be acting on the same pathway to influence hysterectomy, a set of survival models were run in which only parous women were included and these two characteristics were adjusted for each other. In a second set of models including all women, the associations between other reproductive characteristics and hysterectomy found to be significant in unadjusted models, were adjusted for other reproductive characteristics which were associated with hysterectomy.

Likelihood ratio tests were used to test the significance of including the reproductive characteristics tested in adjusted models. In conducting these tests it was ensured that all models compared were nested within each other and were based on the same N.

6.4.4.3 Analyses to address objective (iii) – reason for hysterectomy

Using the competing risks framework described in chapter 3 the association between each reproductive characteristic and subsequent hysterectomy rates by reason for hysterectomy was assessed.

6.5 Results

6.5.1 Results from analyses to address objective (i) - unadjusted associations

Age at menarche was significantly inversely associated with hysterectomy, table 6.1 - women who had an older age at menarche had significantly lower rates of hysterectomy than women with younger ages at menarche. Tests of deviation from linearity were not significant suggesting that this association was linear on the log scale.

In a survival model with follow-up from age at menarche to age 57 years there was significant interaction between age at first birth and time (p=0.001) i.e. the proportional hazards assumption was violated. The Kaplan-Meier graph of the association between age at first birth and hysterectomy, figure 6.1, suggests that this interaction was caused by the methodological problem that amongst a group of women all of whom are known to be parous, women cannot have had their hysterectomy before they have had their children so, women who for example have their first child at age 33 years cannot by definition have had a hysterectomy earlier than this. The result is that when examining hysterectomies performed at early ages women with late age at first birth are by definition at no risk of having had a hysterectomy. The relationship would therefore be expected to change with time once women with later age at first birth have their children and finally become 'at risk' of hysterectomy. To allow for this, attempts to identify two or three piecewise models covering the whole period of follow-up similar to those used in chapter 4 were made. As it was not possible to identify piecewise models covering the entire follow-up time without continuing to violate the proportional hazards assumption in the models covering the time period before all women had had their first child, a survival model was used in which follow-up time started at age 35 years by which time 99.2% of women had had their first child and were therefore 'at risk' of hysterectomy. The results from this analysis, table 6.1, suggest that women with later age at first birth had lower rates of hysterectomy than women with earlier age at first birth and that this association was linear. In this model the test for interaction with time was not significant when age at first birth was entered as a continuous term (p=0.08) and was on the borderline of significance when age at first birth was considered as a categorical variable (p=0.04). Examination of the interaction terms and the Kaplan-Meier graph suggest that the protective effect of later age at first birth weakens with age so the results presented should be considered with caution. However, despite the attenuation in effect over time, at all ages, women with later ages at first birth had lower cumulative rates of hysterectomy than women with younger ages at first birth and the proportion of women who had had a hysterectomy in the group of women with later age at first birth remained lower than the proportion in the group of women with earlier age at first birth across the whole period of follow-up.

Parity was significantly associated with hysterectomy – nulliparous women had lower rates of hysterectomy than parous women, table 6.1 and figure 6.2. The number of children parous women had was also found to be important with women who had more children having higher rates of hysterectomy than women who had fewer children. Figure 6.2 clearly demonstrates that women with ≥3 children had the highest rates of hysterectomy at all ages while women with some but fewer than 3 children had similar hysterectomy rates to each other although these were still higher than the rate amongst nulliparous women. Tests of deviations from linearity were not significant suggesting that the positive association between number of children and hysterectomy rates was linear on the log scale. Similar results to those shown for parity at age 30 years were found when parity at ages 36 and 53 years were examined (results not shown) suggesting that it was appropriate to use parity at age 30 years in the main analyses.

Ever having used OCs and age at first use were not significantly associated with hysterectomy rates, table 6.2. There was a significant reduction in hysterectomy rates associated with each 1 year increase in use of OCs among OC users but whether this was a real effect is difficult to establish.

Most markers of subfertility examined (ever had a stillbirth or miscarriage, ever consulted a doctor or other professional about infertility and length of time between birth of first and second child) were not significantly associated with hysterectomy rates. Table 6.2 shows only the results from the analyses of the binary variables for stillbirth or miscarriage and infertility. When those women who reported multiple stillbirths and/or miscarriages were separated from those women who only reported one such event, and when infertility was categorised by reason there were still no significant differences between categories.

As for age at first birth, there was a significant interaction between suffering from irregular/infrequent menstrual cycles in 20s and/or 30s and time (p=0.002) i.e. the proportional hazards assumption was violated. Study of the Kaplan-Meier graph of the association between irregular/infrequent menstrual cycles and hysterectomy, figure 6.3, suggested that the pattern of association changed approximately 35 years after menarche (i.e. at approximately age 48 years). For this reason the association from age at menarche up to age 48 years and the association from age 48 years to the end of follow-up were examined in separate piecewise models. Women who reported suffering a lot from irregular/infrequent menstrual cycles in their 20s and/or 30s had much higher rates of hysterectomy than women who reported not suffering from either irregular/infrequent periods during their 20s and/or 30s up to age 48 years. However, there was no association between reports of irregular/infrequent menstrual cycles in the 20s and/or 30s and hysterectomy rates between ages 48 and 57 years. There was no evidence that proportional hazards assumptions were being violated in either piecewise model.

6.5.2 Results from analyses to address objective (ii) - adjusted associations

Age at menarche was not significantly associated with any other reproductive characteristic whereas parity and age at first birth were significantly negatively correlated with each other and also associated with most other reproductive characteristics except age at menarche and suffering from irregular or infrequent menstrual cycles. These patterns of association (results not shown) were all plausible and most were in expected directions.

As age at first birth and parity were found to be associated with each other and it was hypothesised that the two factors may not independently predict hysterectomy rates they were entered into the same survival model. The adjusted hazard ratios estimated were difficult to interpret because of collinearity resulting from the significant association between the two variables. Results from likelihood ratio tests comparing a model with both variables included to models with each variable entered individually suggested, as signified by non-significant p-values (results not shown), that there was no benefit in including both variables in the same model as they predicted hysterectomy rates in the same way. It therefore seems likely that in the NSHD age at first birth was associated with hysterectomy rates because it was a marker of parity.

In a second set of models in which the effects of age at menarche and parity were adjusted for each other it was found that the point estimates of effect and significance of these two characteristics were not altered by adjustment for the other factor, table 6.3, suggesting that they predict hysterectomy rates independently of each other. A test for interaction between these two variables was not significant.

In a final set of models in which irregular/infrequent menstrual cycles, the only other characteristic significantly associated with hysterectomy in unadjusted models, was entered into models with parity and age at menarche it was found that with follow-up to age 48 years the effects of all three variables were independent of each other – multiple adjustment did not greatly alter the size of any of the unadjusted hazards ratios and all three factors remained significantly associated with hysterectomy rates (results not shown). The results from the likelihood ratio tests confirmed this, table 6.4, and demonstrated that inclusion of all three variables in a model provided a better fit to the data than inclusion of only one or two of the characteristics. In models with follow-up from age 48 to 57 years there remained no effect of irregular/infrequent menstrual cycles after adjustment for the other two characteristics.

6.5.3 Results from analyses to address objective (iii) – reason for hysterectomy

A significant inverse association between age at menarche and hysterectomy for fibroids was found, table 6.5. For each other group of reasons there were non-significant associations operating in the same direction.

There were no clear differences in the pattern of association between age at first birth, parity and hysterectomy by reason for hysterectomy with associations for each different reason all acting in the same direction as each other, table 6.5. Parous women had significantly higher rates of hysterectomy than nulliparous women for all major groups of reason (i.e. fibroids, menstrual disorders, prolapse and cancer).

Although there was some evidence of variation by reason for hysterectomy in the direction of associations between ever having used OCs, ever having had a stillbirth or miscarriage, the length of time between the birth of the first and second child and hysterectomy none of these associations were significant (results not shown) and grouping all hysterectomies together did not appear to be masking any effects specific to any one or more specific reason.

As expected, given that irregular/infrequent menstrual cycles could be symptoms which women report to their doctor directly resulting in them being offered or requesting a hysterectomy, a strong association between irregular/infrequent menstrual cycles and hysterectomy was found for hysterectomies performed for menstrual disorders with follow-up to age 48 years, table 6.6. Significant associations which acted in the same direction were also found for hysterectomies for prolapse, other known and unknown reasons within the same period of follow-up. There were no significant associations for any reason in models with follow-up from age 48 to 57 years.

6.6 Discussion

6.6.1 Main findings

In unadjusted analyses age at menarche, age at first birth, parity and suffering from irregular/infrequent menstrual cycles in early adulthood were all associated with hysterectomy rates, other reproductive characteristics were not. The directions of these associations were such that women with earlier age at menarche, earlier age at first birth, who were parous and who reported suffering a lot from irregular/infrequent menstrual cycles in their 20s and/or 30s had higher rates of hysterectomy than women with later age at menarche, later age at first birth, who were nulliparous and who did not report irregular/infrequent menstrual cycles, respectively. The associations between hysterectomy and both irregular/infrequent menstrual cycles and age at first birth attenuated with age.

The associations between hysterectomy and age at first birth and parity were not independent of each other with the suggestion that age at first birth was associated with hysterectomy only because of its strong inverse association with parity. The associations between age at menarche, parity and, up to age 48 years, irregular/infrequent menstrual cycles and hysterectomy all remained significant after mutual adjustment suggesting that these three associations were independent of each other.

The association between age at menarche and hysterectomy varied by reason for hysterectomy with a much stronger association found when considering hysterectomies for fibroids than when considering hysterectomy for any other reason. For the other reproductive characteristics associated in unadjusted analyses with hysterectomy rates overall i.e. parity, age at first birth and irregular/infrequent menstrual cycles there was less marked variation in effect by reason for hysterectomy with hysterectomies for different reasons all associated with these characteristics in similar ways.

6.6.2 Comparison with other studies

The results from these analyses are consistent with the findings from other studies detailed in section 6.2.

There was a suggestion from some existing studies[122;128;167] that the association between parity and hysterectomy may not be linear but the analyses of the NSHD suggest a linear effect.

Methodological problems in analysing the associations between hysterectomy and age at first birth, parity and menstrual characteristics were identified in these analyses that had not been reported in other studies. These problems exist because all three characteristics as well as influencing hysterectomy risk could themselves be influenced by hysterectomy. Women cannot suffer from irregular/infrequent menstrual cycles or, have more children once they have had a hysterectomy. Further, if a woman is known to have had children she cannot have had a hysterectomy at any age before these births have occurred. Attempts to overcome these problems were successfully made by using parity at age 30 years, irregular/infrequent menstrual cycles reported in women's 20s and 30s with follow-up time split in two and running analyses of age at first birth with follow-up from age 35 years. That no other study has identified or attempted to deal with these methodological challenges is partly because so many existing studies are cross-sectional and have used logistic regression instead of survival analysis.

6.6.3 Explanation of findings

As a caveat, there are limits to how far the results from this chapter should be interpreted given most analyses were unadjusted except for each other, a limitation which will be addressed in the next chapter. However, even without adjustment for other variables the findings from these analyses are informative.

Age at menarche, parity and irregular/infrequent menstrual cycles were independently associated with hysterectomy suggesting that they operate on different pathways to influence hysterectomy risk. The independence of these three characteristics from each other and the lack of association between other reproductive factors and hysterectomy suggests that they are not influencing hysterectomy because they are parts of the same composite measure of reproductive function, a characteristic which cannot be measured directly but which all the variables considered in this chapter either influence or indicate.[262]

6.6.3.1 Age at menarche

The results appear to implicate one particular pathway between age at menarche and hysterectomy – the association with oestrogen exposure. Age at menarche is one of the main influences on the length of time across life during which a woman is exposed to oestrogen, with women who have an earlier age at menarche regularly exposed to oestrogen and other endogenous hormones from an earlier age and therefore for a longer duration by the time they reach middle-age. In addition, it has been found that women with earlier age at menarche may be exposed to higher concentrations of oestrogen across life than women with later age at menarche.[263;264] Higher levels of exposure to unopposed oestrogen are associated with the development of some major gynaecological conditions, most importantly fibroids,[20] one of the most common reasons for hysterectomy. That women in the NSHD who had earlier ages at menarche had higher rates of hysterectomy and, that this association was significant for hysterectomies for fibroids supports the notion that age at menarche influences hysterectomy risk through its association with oestrogen exposure.

Some other theoretically plausible pathways between age at menarche and hysterectomy can be discounted by the analysis findings. As age at menarche was not associated with age at first birth or parity its association with hysterectomy cannot be mediated by these other reproductive characteristics. Likewise although an association between age at menarche and hysterectomy could be explained by infertility or subfertility - late age at menarche can be a marker of gynaecological development problems, problems which could influence fertility and subsequent risk of hysterectomy - as infertility and markers of subfertility were not associated with age at menarche or hysterectomy in the NSHD this explanation can be discounted. In Hardy and Kuh's model of the pathways to hysterectomy (reproduced in chapter 3, figure 3.4) it was proposed that age at menarche could be associated with hysterectomy through its association with menstrual characteristics. However, irregular/infrequent menstrual cycles were not associated with age at menarche in the NSHD and the effects of these two characteristics on hysterectomy were independent of each other. In other analyses (results not shown) age at menarche did not predict a number of different menstrual characteristics providing further evidence that this pathway was not operating.

That most other plausible pathways can be discounted provides further support for the suggestion that age at menarche was associated with hysterectomy rates because of its association with oestrogen exposure. What does need to be considered and cannot be discounted by the results from analyses so far is that age at menarche and body weight may be acting on the same pathways to influence hysterectomy risk. Analyses in the previous chapter found evidence of an association between BMI in adulthood and subsequent hysterectomy rates and in another study age at menarche has been found to predict adult BMI independent of childhood BMI.[256] This will be investigated further in the next chapter.

6.6.3.2 Parity

Unlike age at menarche, parity acts in the opposite direction to that which would be expected if it was associated with hysterectomy via an association with oestrogen exposure, other pathways must therefore explain the association found. A number of pathways between parity and hysterectomy are plausible and could explain the association in the direction found. With each additional birth, the likelihood of damage to gynaecological and pelvic organs having occurred and, the amount of damage suffered is likely to increase resulting in greater medical need for hysterectomy among women with higher parity. While this explanation cannot be fully discounted by the results, this pathway would be unlikely to result in associations between parity and hysterectomies for each different reason which are as similar as found.

An association between increases in BMI across adulthood and subsequent hysterectomy rates was found in the previous chapter and studies show that increased parity is associated with subsequent increases in body weight,[201;208] suggesting that BMI and parity could be acting on the same pathway to influence risk of hysterectomy. This will be investigated in the next chapter.

While the two pathways described above are plausible, the lack of a difference in the effect of parity on hysterectomy by reason, despite parity being protective against some gynaecological disorders including fibroids[20;265;266] and endometrial cancer,[267] having no independent effect on other disorders including menorrhagia[268] and a risk factor for others including prolapse,[269] suggests that social or decision making pathways between parity and hysterectomy may be more important than pathways which influence medical need. Women with greater numbers of children would be expected to be more likely than other women to request a hysterectomy to prevent further pregnancies, be less likely to decline the offer of a hysterectomy in order to preserve their fertility and may be more likely to be offered a hysterectomy by a doctor because of the reduced need perceived by the doctor to preserve fertility. This is supported by evidence from a study of women's treatment preferences for menstrual problems in which nulliparous women found the idea of losing their fertility as a consequence of hysterectomy to be less acceptable than parous women.[270] As parity is socioeconomically graded it is possible that SEP could be acting on the same pathway as parity to influence risk of hysterectomy and this will be investigated in the next chapter.

6.6.3.3 Irregular/infrequent menstrual cycles

The most likely reason for finding that women who reported suffering a lot from irregular/infrequent menstrual cycles during their 20s and/or 30s experienced higher rates of hysterectomy up to age 48 years is because these symptoms would have directly resulted in women consulting their doctor and, if the symptoms were severe, being offered a hysterectomy. This explanation is supported by the fact that the association between irregular/infrequent menstrual cycles and hysterectomy was strongest on hysterectomies for menstrual disorders and that the association attenuated with age and was only found for hysterectomies performed close to the age when symptoms were reported. Other possible pathways involving associations with parity and fertility levels can be discounted as no association between parity and irregular/infrequent menstrual cycles was found and the associations between these two factors and hysterectomy were independent of each other.

6.6.3.4 Other reproductive characteristics

For all other reproductive characteristics i.e. stillbirth/miscarriage, OC use, infertility and length of time between birth of first and second child, there was no association with hysterectomy for any reason. This lack of associations could have been found because there were no real associations between these factors and hysterectomy or because any effect is small and has not been detected due to a lack of power. Alternatively, it could be that the measures of these reproductive characteristics used were not valid. Infertility and stillbirth/miscarriage were measured at only one time using very basic questions and, information on OC use was collected only twice. More importantly all measures were self-reported and not validated despite the fact that some measures may not be reliably recalled e.g. duration of OC use.[271]

Time between birth of first and second child was included in analyses as a marker of subfertility because in populations of sexually active women not using contraceptives a gap between two births of greater than five years suggests subnormal fertility. However, in the NSHD, as in most other modern cohorts, women have much more control over the number and timing of their births using contraceptives, which are commonly used. Further it cannot be assumed that all women in the cohort will have been sexually active at all times in adulthood and so long gaps between births may be acting as an indicator of characteristics other than subfertility which may not be associated with hysterectomy in the NSHD. Stillbirth/miscarriage was also included as a marker of subfertility but in analyses of the associations between the different reproductive characteristics in the NSHD, experience of a stillbirth or miscarriage was associated with higher parity than no experience of stillbirth or miscarriage. This suggests that women in the NSHD who experienced a stillbirth/miscarriage were not those who were subfertile but were those with greater exposure to pregnancy and therefore with a greater chance of experiencing a negative pregnancy outcome over their reproductive lives.

6.6.4 Limitations

The potential lack of both power and validity in analyses of some of the reproductive characteristics described above are two potential limitations of the data. However, these limitations do not affect analyses of all reproductive characteristics examined as some significant effects were detected and measures such as parity and age at menarche are expected to be valid.

There are other limitations which are specific to particular analyses. It is not possible to separate out the effects of stillbirth and miscarriage from each other or investigate the effect of the timing of these because of the limited number of questions which were asked about these events and so this relationship could not be examined in more detail.

Further, there are other characteristics which it may have been useful to examine but which because the data has not been collected it was not possible to consider. Such factors include induced abortion, information which is not held because information on this was considered too sensitive to request and is unlikely to have been reliably reported especially as abortion was illegal in the UK until 1968 by which time the women were 22 years old.

To address some of the limitations of the data more appropriate measures of both infertility and subfertility could be ascertained by collecting retrospective information on time to pregnancy,[272] an improvement compared to the existing measures of subfertility as it allows for the fact that not all women are having unprotected intercourse at all times across their reproductive lives. Further information on stillbirths and miscarriages so that these two events can be separated out would also be informative as would information, possibly from general practice records, to improve or validate the existing data on OC use.

6.6.5 Strengths

Despite having limitations, these analyses do have important strengths compared to existing studies. Firstly, the wide range of reproductive characteristics studied has made it possible to recognise which pathways to hysterectomy may be important and identify important differences between the associations with hysterectomy of different reproductive characteristics. This has been achieved not only because of the range of characteristics studied but also because it has been possible to analyse the associations by reason for hysterectomy which only two other studies[1;137] have done previously and, in these two studies very few characteristics were considered. Further, because survival analyses were used and the temporal nature of the different associations was considered, important methodological challenges (detailed above) were identified which other studies have failed to detect.

The original cohort was selected to be nationally representative whereby the results from these analyses may be more generalisable than results from other studies. Although selective loss to follow-up could have introduced bias and reduced the generalisability of findings, comparisons of those women included in analyses with those women not included (results not shown) found no significant differences between the two groups in the distribution of reproductive characteristics with the exception of parity and age at first birth.

6.6.6 Conclusions

Some reproductive characteristics i.e. age at menarche, parity and irregular/infrequent menstrual cycles were associated with hysterectomy in the NSHD. Caution in interpreting these results is needed as no adjustments for other variables including SEP and BMI have been made. The associations between these reproductive characteristics and other potential predictors of hysterectomy are examined in the following chapter after which it will be possible to draw more detailed conclusions and consider the implications of the findings.

Figure 6.1: Kaplan-Meier survival estimates for hysterectomy by age at first birth in the NSHD (N = 1,543)

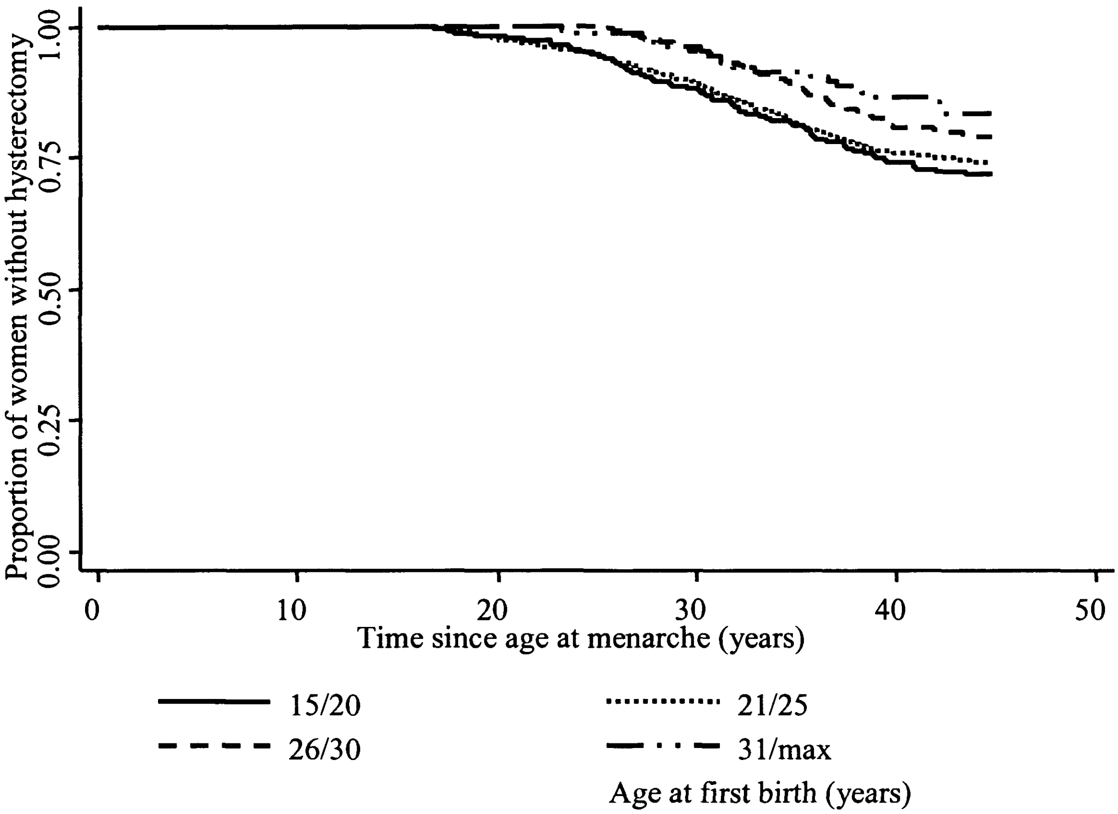


Figure 6.2: Kaplan-Meier survival estimates for hysterectomy by parity at age 30 years in the NSHD (N = 1,746)

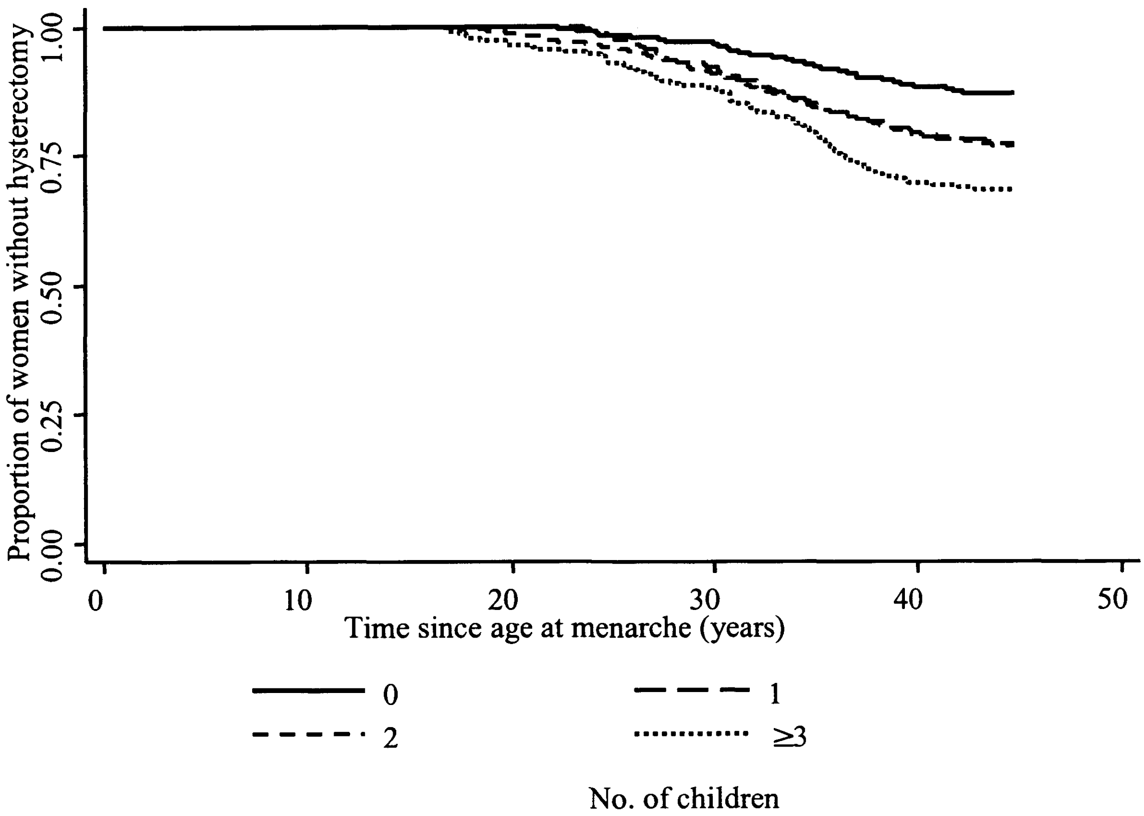


Figure 6.3: Kaplan-Meier survival estimates for hysterectomy by irregular or infrequent menstrual cycles in the NSHD (N = 1,193)

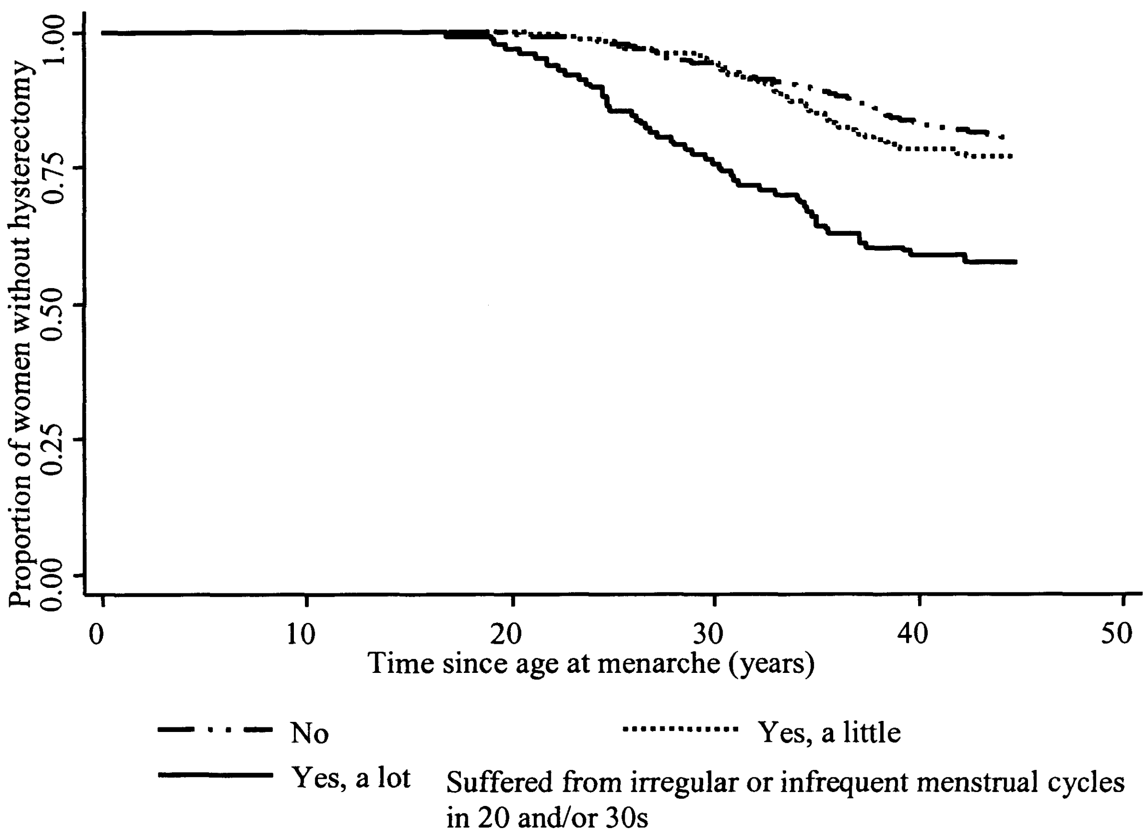


Table 6.1: Unadjusted survival analyses of the associations between reproductive characteristics and hysterectomy in the NSHD

Reproductive characteristic	N (%) [No. of hysterectomies]	Hysterectomy rate per 1000 women years (95% CI)	Hazard Ratio for hysterectomy (95% CI)	p-value
Age at menarche (years) (N=1434)				
9 – 11	235 (16.39) [58]	6.14 (4.74, 7.94)	1.00	0.03*
12	397 (27.68) [100]	6.23 (5.12, 7.57)	1.01 (0.73, 1.40)	0.01**
13	487 (33.96) [104]	5.25 (4.33, 6.36)	0.84 (0.61, 1.16)	
14 and above	315 (21.97) [52]	3.99 (3.04, 5.23)	0.63 (0.43, 0.92)	
per 1 year increase†	1384 (100) [308]	5.46 (4.89, 6.11)	0.88 (0.80, 0.96)	0.005*
Age at first birth (years) (N=1505) [follow-up from 35 years]				
15 – 20	358 (23.78) [89]	14.24 (11.57, 17.53)	1.00	0.09*
21 – 25	647 (42.99) [144]	12.09 (10.27, 14.24)	0.85 (0.65, 1.11)	0.01**
26 – 30	378 (25.12) [78]	10.74 (8.60, 13.40)	0.76 (0.56, 1.02)	
≥31	123 (8.17) [20]	8.31 (5.36, 12.88)	0.58 (0.36, 0.95)	
per 1 year increase	1505 (100) [331]	11.90 (10.68, 13.25)	0.97 (0.94, 0.99)	0.01*
Parity at age 30 years (N=1746)				
Nulliparous	326 (18.67) [43]	3.13 (2.32, 4.22)	1.00	<0.0001*
Parous	1420 (81.33) [349]	6.12 (5.51, 6.79)	2.04 (1.49, 2.81)	
No. of children 0	326 (18.67) [43]	3.13 (2.32, 4.22)	1.00	<0.0001*
1	339 (19.42) [76]	5.50 (4.39, 6.89)	1.82 (1.25, 2.64)	<0.001**
2	741 (42.44) [168]	5.60 (4.82, 6.52)	1.86 (1.33, 2.60)	
≥3	340 (19.47) [105]	7.93 (6.55, 9.60)	2.72 (1.91, 3.88)	
per 1 child increase$^{\Phi}$	1420 (100) [349]	6.12 (5.51, 6.79)	1.22 (1.08, 1.38)	0.001*

† Total N less than N for analysis of age at menarche as a categorical variable as women with unknown age at menarche who were known not to have reached menarche by age 14 were included in the upper category but were excluded from analyses of age at menarche as a continuous variable

Φ Nulliparous women excluded

* p-value from likelihood ratio test

** p-value from test for trend

Table 6.2: Unadjusted survival analyses of the associations between reproductive characteristics and hysterectomy in the NSHD

Reproductive characteristic		N (%) [No. of hysterectomies]	Hysterectomy rate per 1000 women years (95% CI)	Hazard Ratio for hysterectomy (95% CI)	p-value
Oral contraceptive use (N=1693)					
Ever used	No	341 (20.14) [72]	5.19 (4.12, 6.54)	1.00	0.62*
	Yes	1352 (79.86) [303]	5.52 (4.93, 6.18)	1.07 (0.82, 1.38)	
Duration of use (yrs)	0	341 (20.14) [72]	5.19 (4.12, 6.54)	1.00	0.26*
	1 – 5	741 (43.77) [183]	6.14 (5.31, 7.09)	1.19 (0.91, 1.57)	0.95**
	6 – 10	311 (18.37) [62]	4.88 (3.81, 6.26)	0.94 (0.67, 1.32)	
	11 – 15	145 (8.56) [25]	4.14 (2.80, 6.12)	0.78 (0.50, 1.23)	
	16 – 30	60 (3.54) [12]	4.86 (2.76, 8.55)	0.92 (0.50, 1.70)	
	Used for unknown duration	95 (5.61) [21]	5.41 (3.53, 8.30)	1.05 (0.65, 1.71)	
	per 1 year increase†	1257 (100) [282]	5.53 (4.92, 6.21)	0.97 (0.94, 0.99)	0.01*
Age at first use (yrs)	Never used	341 (20.14) [72]	5.19 (4.12, 6.54)	1.00	0.78*
	15 – 20	224 (13.23) [58]	6.45 (4.99, 8.35)	1.26 (0.89, 1.78)	0.99**
	21 – 25	769 (45.42) [164]	5.23 (4.49, 6.10)	1.01 (0.76, 1.33)	
	26 – 30	214 (12.64) [50]	5.76 (4.37, 7.60)	1.11 (0.78, 1.59)	
	> 30	54 (3.19) [11]	5.01 (2.77, 9.04)	0.97 (0.51, 1.83)	
	Used but age at first use unknown	91 (5.38) [20]	5.41 (3.49, 8.38)	1.06 (0.64, 1.73)	
	per 1 year increase$^{\Phi}$	1261 (100) [283]	5.53 (4.92, 6.21)	0.99 (0.96, 1.03)	0.75*
Ever had a stillbirth or miscarriage (N=1613)					
	No	1247 (77.31) [273]	5.39 (4.79, 6.07)	1.00	0.25*
	Yes	366 (22.69) [91]	6.18 (5.04, 7.59)	1.15 (0.91, 1.46)	
Ever consulted a doctor or other professional about infertility (N=1605)					
	No	1440 (89.72) [328]	5.63 (5.05, 6.27)	1.00	0.74*
	Yes	165 (10.28) [36]	5.34 (3.85, 7.40)	0.94 (0.67, 1.33)	
Length of time between birth of first and second child (N=1272)					
	≤5 years	1185 (93.16) [286]	5.99 (5.34, 6.73)	1.00	0.79*
	> 5 years	87 (6.84) [20]	5.66 (3.65, 8.78)	0.94 (0.60, 1.48)	
Irregular or infrequent menstrual cycles in 20s and/or 30s					
Follow-up to age 48 years (N = 1193, no. of hysterectomies = 172)					
	No	857 (71.84) [96]	3.24 (2.65, 3.96)	1.00	<0.0001*
	Yes, a little	213 (17.85) [32]	4.35 (3.07, 6.15)	1.35 (0.90, 2.01)	
	Yes, a lot	123 (10.31) [44]	11.04 (8.21, 14.83)	3.82 (2.67, 5.46)	
Follow-up from age 48 to 57 years (N = 1021, no. of hysterectomies = 94)					
	No	761 (74.53) [69]	10.90 (8.61, 13.80)	1.00	0.93*
	Yes, a little	181 (17.73) [17]	11.31 (7.03, 18.19)	1.05 (0.62, 1.78)	
	Yes, a lot	79 (7.74) [8]	12.72 (6.36, 25.43)	1.15 (0.55, 2.40)	

† Never users and women with unknown duration of use excluded
Φ Never users and women with unknown age at first use excluded
* p-value from likelihood ratio test
** p-value from test for trend

Table 6.3: Survival analyses of the associations between hysterectomy and age at menarche and parity at age 30 years adjusted for each other (N=1354, no. of hysterectomies=304)

Variables included in the model	Unadjusted Hazard Ratio for hysterectomy (95% CI)	Hazard Ratio for hysterectomy (95% CI) adjusted for other variable
Age at menarche		
per 1 year increase	0.87 (0.80, 0.96)	0.87 (0.79, 0.95)
p-value	*0.004*	*0.003*
Parity		
per 1 child increase	1.29 (1.16, 1.43)	1.29 (1.17, 1.43)
p-value	*<0.001*	*<0.001*

Table 6.4: Comparison of Cox regression models including irregular/infrequent menstrual cycles, parity and age at menarche with follow-up to age 48 years

Variables included in model 1 (H_A)	Variables included in model 2 (H_0)	p-value from likelihood ratio test comparing models 1 and 2	Which model provides the best fit?
N=956, no. of hysterectomies=135			
Age at menarche; Irregular periods	Age at menarche	<0.0001	Model 1
Age at menarche; Irregular periods	Irregular periods	0.008	Model 1
N=934, no. of hysterectomies=132			
Age at menarche; Irregular periods; Parity at 30	Age at menarche; Irregular periods	0.006	Model 1
Age at menarche; Irregular periods; Parity at 30	Age at menarche; Parity at 30	<0.0001	Model 1
Age at menarche; Irregular periods; Parity at 30	Irregular periods; Parity at 30	0.01	Model 1

H_A Alternative hypothesis: the more complex model fits the data most appropriately
H_0 Null hypothesis: the simpler model fits the data most appropriately
Model 2 is nested within model 1

Table 6.5: Unadjusted survival analyses of the associations between reproductive characteristics and hysterectomy by reason for hysterectomy in the NSHD

Reproductive characteristic	Hazard Ratio for hysterectomy for specified reason (95% CI) [No. of hysterectomies]					
	Fibroids	**Menstrual disorders**	**Prolapse**	**Cancer**	**Other**	**Unknown**
Age at menarche (N=1384)	[N=98]	[N=88]	[N=30]	[N=22]	[N=47]	[N=23]
per 1 year increase	0.80 (0.68, 0.94)	0.91 (0.77, 1.09)	0.89 (0.66, 1.19)	0.83 (0.59, 1.18)	0.95 (0.75, 1.19)	0.98 (0.71, 1.36)
p-value	*0.006*	*0.31*	*0.42*	*0.30*	*0.64*	*0.90*
Age at first birth† (N=1505)	[N=112]	[N=95]	[N=35]	[N=19]	[N=41]	[N=29]
per 1 year increase	0.98 (0.94, 1.03)	0.94 (0.90, 0.99)	0.98 (0.91, 1.06)	0.94 (0.84, 1.05)	0.93 (0.86, 1.01)	1.01 (0.93, 1.10)
p-value	*0.48*	*0.02*	*0.60*	*0.27*	*0.07*	*0.82*
Parity at age 30 years (N=1746)	[N=123]	[N=113]	[N=38]	[N=26]	[N=57]	[N=35]
Nulliparous	1.00	1.00	1.00	1.00	1.00	1.00
Parous	2.15 (1.21, 3.82)	2.29 (1.23, 4.27)	4.71 (1.13, 19.57)	6.24 (0.85, 46.05)	1.33 (0.65, 2.71)	1.01 (0.44, 2.32)
p-value	*0.004*	*0.004*	*0.007*	*0.02*	*0.42*	*0.98*
(N=1420)	[N=110]	[N=102]	[N=36]	[N=25]	[N=48]	[N=28]
per 1 child increase$^{\Phi}$	1.06 (0.85, 1.32)	1.18 (0.94, 1.47)	1.35 (0.93, 1.94)	1.42 (0.93, 2.17)	1.35 (0.99, 1.84)	1.50 (1.01, 2.22)
p-value	*0.62*	*0.16*	*0.12*	*0.10*	*0.07*	*0.06*

† Follow-up from age 35 years
Φ Nulliparous women excluded

Table 6.6: Unadjusted survival analyses of the association between irregular/infrequent menstrual cycles and hysterectomy by reason for hysterectomy in the NSHD

Irregular or infrequent menstrual cycles in 20s and/or 30s	Hazard Ratio for hysterectomy for specified reason (95% CI) [No. of hysterectomies]					
	Fibroids	Menstrual disorders	Prolapse	Cancer	Other	Unknown
Follow-up from age at menarche to age 48 years						
(N=1193)	[N=54]	[N=59]	[N=10]	[N=10]	[N=28]	[N=11]
No	1.00	1.00	1.00	1.00	1.00	1.00
Yes, a little	1.01 (0.49, 2.10)	2.10 (1.10, 4.00)	no hysterectomies	no hysterectomies	3.03 (1.28, 7.19)	no hysterectomies
Yes, a lot	2.11 (1.02, 4.39)	5.58 (3.07, 10.13)	3.53 (0.91, 13.66)	0.91 (0.11, 7.15)	4.73 (1.86, 12.02)	10.14 (3.09, 33.28)
p-value	*0.17*	*<0.001*	*0.04*	*0.14*	*0.003*	*0.0002*
Follow-up from age 48 to 57 years						
(N=1021)	[N=41]	[N=12]	[N=17]	[N=3]	[N=15]	[N=6]
No	1.00	1.00	1.00	1.00	1.00	1.00
Yes, a little	1.37 (0.65, 2.91)	0.94 (0.20, 4.35)	0.65 (0.15, 2.89)	no hysterectomies	0.65 (0.15, 2.90)	2.81 (0.47, 16.79)
Yes, a lot	1.41 (0.50, 4.02)	1.11 (0.14, 8.74)	1.54 (0.35, 6.81)	no hysterectomies	no hysterectomies	3.28 (0.34, 31.57)
p-value	*0.64*	*0.99*	*0.69*	*n/a*	*0.26*	*0.43*

Chapter 7: The inter-relationship between predictors of hysterectomy

Main objective: To investigate the inter-relationship between predictors of hysterectomy in the NSHD

7.1 Introduction

In the previous three chapters it was shown that education, BMI across adulthood, age at menarche, parity and reports of irregular/infrequent menstrual cycles were associated with hysterectomy risk in the NSHD. Until now, caution in interpreting these findings has been required as the independence of these three different but potentially inter-related sets of factors from each other has not been investigated. This chapter aims to address this shortcoming.

7.2 Framework

The framework for analysis of the predictors of hysterectomy in chapter 3 (figure 3.5) omitted the potential lines of association between SEP, weight and reproductive characteristics so as not to overcomplicate the diagram. In light of the findings from chapters 4 to 6 some of the factors and pathways shown in this original figure can be removed as it has been demonstrated that they were not significantly associated with hysterectomy in the NSHD. The potential lines of association between all the different factors found to be associated with hysterectomy in this thesis is now shown, see figure 7.1. Each predictor in this framework and its potential relationship with other predictors in relation to hysterectomy is described below. This will provide the justification for inclusion of the lines of association shown in figure 7.1 and investigated in the following analyses. It should be noted that irregular/infrequent menstrual cycles are not included in the framework as they appeared to be acting as a direct marker of medical need for hysterectomy.

7.3 Mediators or confounders?

If two factors are associated with an outcome, in this case hysterectomy, and also associated with each other it is possible that they do not act independently of each other to influence risk of the outcome. As discussed by Singh-Manoux,[273] with specific reference to pathways between indicators of SEP and health but equally applicable to studies of the association between other explanatory variables and health outcomes, there are a number of well recognised ways in which two associated factors could operate to influence an outcome. Figure 7.2 is a reproduction of three pathways described. In a hypothetical situation where there is a main explanatory variable X, another explanatory variable A which is associated with X and, both X and A are associated with the outcome Y it is possible that A and X act independently of each other to influence Y. It is also possible, dependent on the temporal relationship between X and A, that: a single variable (A) or a series of variables (A1, A2, A3 etc.) mediate the association between X and Y (figure 7.2, model 1); A moderates/modifies the effect of the association between X and Y (figure 7.2, model 2); A confounds the association between X and Y (figure 7.2, model 3).

While it is possible to test whether one variable moderates the association between another variable and the outcome formally using tests for interaction there is not a statistical test which enables epidemiologists to distinguish between confounding and mediation. The presence of confounding and mediation are detected using the same method – adjustment of the association of interest for the potential confounder/mediator. If the size of the association between X and Y is altered after adjustment for A this suggests that A confounds or mediates the association between X and Y but does not suggest which of these scenarios is operating. Distinguishing between confounding and mediation is a methodological challenge which it is important to try and overcome given the different implications of and conclusions which can be drawn dependent on whether an association is thought to be confounded or mediated by another factor. Given traditional statistical tests do not allow us to make this distinction it is necessary to consider other ways to do this. One way is to consider the temporal relationship between the two explanatory factors. If A is antecedent to X, the association between X and the outcome Y cannot be mediated, by definition, by A. However in this situation, the association between X and Y could be confounded by A or the association between A and Y could be confounded or mediated by

X, the most likely of which would be determined by studying which of the associations with Y is altered after adjustment for the other variable. Another way of trying to distinguish between confounding and mediation is simply to consider which explanation seems most plausible.

7.4 The associations between the different predictors of hysterectomy

For simplicity, the associations between pairs of predictors are considered below. It will be possible to consider more complex patterns of association between a wider number of predictors once the pairs of predictors which are associated with each other and appear to have an overlapping influence on hysterectomy risk have been identified.

7.4.1 Educational level

Educational level was inversely associated with hysterectomy up to age 44 years in the NSHD. This association could be explained by the direct influence of education on supply and demand factors as discussed in chapter 4. While such pathways are likely to be operating, the fact that there appeared to be differences in the direction of association by reason for hysterectomy suggest that other pathways may also have been operating.

Of the other predictors examined in this thesis, it is plausible that education could be acting to influence hysterectomy risk through an association with body weight and/or parity, figure 7.1. It has been consistently shown, in the NSHD and other studies, that educational level and other indicators of SEP are associated with body weight - women who have lower educational levels have greater risk of obesity and weight gain across adulthood than women with higher educational levels.[113;236;274] It has been proposed that this association could be acting in either or both directions.[275] Women of lower educational level have been found to be more likely to adopt less healthy lifestyles which promote weight gain (i.e. poorer diet and less exercise) than women of higher educational level.[274;276] As well as low educational level indirectly promoting higher body weight it has also been proposed that body weight may influence SEP and that people who are overweight or obese are less likely to attain a high educational level and more likely to suffer from downward social mobility than people of lower weight.[113;275]

Educational level is also associated with parity. Analyses of data from the NSHD have shown that women who had higher educational levels had later ages at first birth and were more likely to be nulliparous at age 36 years than women with lower educational levels.[112;277] Analyses of the association between educational level and parity at age 53 years (results not shown) confirm the maintenance of this association with increasing age i.e. women with higher educational levels did not achieve the same parity as women of lower educational levels at later ages.

While it is possible that the effect of education, because of its association with body weight and parity, is simply mediated or confounded by one or both of these other factors it is also possible that the relationship is more complex than that. As shown in figure 7.1 a number of pathways starting with education can be traced via weight at different time points in adulthood and parity to hysterectomy, for example, education could influence weight in early adulthood which in turn could influence parity, parity may then influence supply and demand factors for hysterectomy and also weight in later adulthood which could itself influence medical need for hysterectomy.

While the association between education and hysterectomy could be mediated or confounded by factors later in life i.e. parity and weight in adulthood, it is also possible that the association between education and hysterectomy is explained by factors in earlier life i.e. age at menarche. There is evidence that age at menarche was associated with educational ability and attainment in the NSHD - females who reached menarche earlier had higher cognitive ability, achieved better grades in their GCE 'O' level exams and were more likely to stay at school until later ages than females who reached menarche later.[278;279] As age at menarche is antecedent to attainment of final educational level, age at menarche cannot mediate the association between education and hysterectomy, it could however confound it. Given early age at menarche is associated with higher educational attainment and higher risk of hysterectomy whereas higher educational attainment is associated with lower risk of hysterectomy if there is a confounding effect of age at menarche on the association between education and hysterectomy it is likely to be negative.

In addition to the possibility that the association between education and hysterectomy risk is mediated or confounded by other predictors examined in this thesis, there could be other unidentified factors which influence medical need for hysterectomy and which are associated with education and could therefore mediate or confound the association. Such factors will be considered later in this chapter once the association between education, parity, weight and age at menarche in relation to hysterectomy risk has been established.

7.4.2 Parity

Nulliparous women in the NSHD had lower rates of hysterectomy than parous women. As discussed in chapter 6, the most likely explanation of this association is that parity influenced hysterectomy risk through its direct influence on supply and demand factors e.g. decision making. It seems likely that women and their doctors are going to be less concerned about the need to preserve fertility when choosing a treatment option if the woman already has children and that this concern will be reduced further the more children a woman has. It is also possible that women who have high parity actively seek or prefer treatment options which end reproductive life to avoid risk of further pregnancy.

In addition to a direct pathway between parity and hysterectomy it is also possible, as shown in figure 7.1, that there are other pathways operating to influence hysterectomy risk on which parity acts. As described in the section above, parity is associated with educational level and the existence of this association implies that parity could mediate or confound the association between education and hysterectomy. While the association between parity and hysterectomy is unlikely to be mediated by education given the temporal relationship between education and parity it is possible that the association between parity and hysterectomy is confounded by education.

Parity is also associated with body weight and so these two factors could be operating on the same pathway to hysterectomy, along with or independently of education. The relationship between parity and body weight is potentially complex and changes with age. There is evidence to suggest that fertility and hence parity may be influenced by body weight in adolescence and early adulthood as women who are at either extreme of weight (i.e. who are underweight or obese) are more likely to be infertile or subfertile than women whose weight is mid-range.[216;220;221;280] BMI later in adulthood has also been found to be associated with parity but this relationship is different. In the NSHD and other studies, there is a positive association between parity and body weight in later adulthood i.e. women who had higher parity had higher body weight which appears to be because the more children a woman has the greater her weight gain across adulthood.[208;236;281] Although it has been suggested that this association could be explained by confounding, the independence of this association from socioeconomic and other reproductive factors has been demonstrated.[208] Physiological changes that occur with pregnancy and/or lifestyle changes (e.g. changes in diet and exercise) which result from living with children are both potential explanations of the association.[208;281] As described in chapter 5, the association between parity and subsequent weight means that in later adulthood the group of women who are overweight and obese will include women who were of normal weight in earlier adulthood, who have high parity and so have gained weight across adulthood and, also women who have been overweight or obese since early adulthood and consequently had no or few children. Analysis of data from the NSHD supports this – at age 36 years women who were nulliparous and women with three or more children were more likely to be obese than women with 1 or 2 children.[236] The change in the pattern of the association between parity and body weight with increasing age means that there are a range of possible pathways which could be operating between these different factors and hysterectomy. The most simple of these is that the effect of body weight in early adulthood is mediated or confounded by parity, that the effect of parity is mediated or confounded by body weight in later adulthood or that the effect of body weight in later adulthood is confounded by parity. More complicated possibilities are that weight in early adulthood influences parity which influences supply and demand factors and also weight in later adulthood which also affects hysterectomy risk. The possibility that parity and body weight operate on the same pathway to hysterectomy, is supported by the fact that there is no variation in association between either of these factors and hysterectomy by reason for hysterectomy, both appear to have effects which operate at all ages rather than attenuating with age like education and, there are changing associations between parity and weight with age and also between weight and hysterectomy with age of BMI measurement.

7.4.3 Age at menarche

Results from chapter 6 suggested that there was an inverse association between age at menarche and hysterectomy. The direction of association, independence of the association from other reproductive characteristics and the variation in association by reason for hysterectomy suggested that age at menarche was associated with hysterectomy most likely through its association with oestrogen exposure.

In addition to the direct biological pathway potentially operating between age at menarche and hysterectomy it is also possible that the association is mediated or confounded by other factors. Education has already been mentioned above. In addition to the possibility that age at menarche confounds the association between education and hysterectomy it is also possible that the association between age at menarche and hysterectomy is mediated or confounded by education. Although an association between education, age at menarche and hysterectomy is plausible, the differences in patterns of association between education and hysterectomy and age at menarche and hysterectomy suggest that this is unlikely to be the only pathway on which either one of these two predictors operate.

Age at menarche is also associated with body weight. There is consistent evidence to show that women who reach menarche earlier have greater risk of high body weight in adulthood compared to women who reach menarche later.[113;256;282;283] There is some debate about whether this association is independent of childhood weight and other confounding factors given childhood weight predicts age at menarche[284;285] and also predicts adult body weight. However some studies have found that the association between age at menarche and adult weight is maintained after adjustment for childhood weight and other potential confounders.[256] The association between age at menarche and hysterectomy could thus be mediated or confounded by adult body weight.

7.4.4 Body weight

There was an n-shaped relationship between BMI in early adulthood and subsequent hysterectomy rates whereas in later adulthood there was a positive linear association between BMI and subsequent hysterectomy rates in the NSHD. Weight gain across adulthood also appeared to predict hysterectomy. As discussed in chapter 5, there could be an association between body weight across adulthood and hysterectomy risk because weight directly influences the risk of developing gynaecological disorders, although there is no evidence that such an explanation is correct. An alternative explanation was that body weight and weight gain indicate the presence of existing gynaecological conditions. This is plausible given suffering from gynaecological symptoms could detrimentally affect diet and activity levels and hence body weight, however, this did not seem to be an adequate explanation of the n-shaped association between BMI in early adulthood and hysterectomy. A further possibility is that an association has been found between body weight and hysterectomy because of an association between body weight and education, parity, age at menarche and/or unidentified factors. Given both age at menarche and education are antecedent to adult body weight they could confound the association between body weight and hysterectomy but not mediate it. However, parity could confound or mediate the association between adult BMI and hysterectomy and this seems to be the most likely of the identified factors to be acting on a common pathway as discussed in section 7.4.2.

7.5 Specific objectives of the chapter

The specific objectives to be addressed in this chapter are:

i. to examine whether the association between educational level and hysterectomy is confounded by age at menarche or is mediated/confounded by parity and/or body weight in adulthood
ii. to examine whether the association between age at menarche and hysterectomy is mediated/confounded by educational level or body weight in adulthood
iii. to examine whether the association between parity and hysterectomy is confounded by educational level or is mediated/confounded by body weight in adulthood
iv. to examine whether the association between body weight and hysterectomy is confounded by age at menarche or educational level or is mediated/confounded by parity
v. to assess the overall level of inter-relationship between the predictors of hysterectomy in the NSHD

7.6 Methods

7.6.1 Main outcome variable

Hysterectomy with or without oophorectomy

7.6.2 Main explanatory variables

Educational level at age 26 years, age at menarche, parity at age 30 years and BMI at ages 26, 43 and 53 years

7.6.3 Ascertainment of explanatory variables

The ascertainment of educational level is described in chapter 4, BMI at ages 26, 43 and 53 years in chapter 5 and age at menarche and parity at age 30 years in chapter 6. Age at menarche and measures of BMI were included in models as continuous variables. All measures of BMI were centred at 20 and, for BMI at ages 26 and 43 years a quadratic term was included because of the evidence in chapter 5 that the association between BMI at these ages and subsequent hysterectomy rates was non-linear. Educational level was categorised into 5 groups as in chapter 4 and parity was categorised into 4 groups as in chapter 6 (i.e. No children; 1; 2; ≥3 children).

7.6.4 Analyses

Many of the same analyses were used to address the different objectives, for example, the same statistical models could be used to test objective (i) whether age at menarche confounds the association between educational level and hysterectomy and objective (ii) whether the association between age at menarche and hysterectomy is mediated or confounded by educational level. For this reason the analyses used to address all objectives are described together.

To be able to clearly identify the individual predictors which had an effect on the association between other predictors and hysterectomy, predictors were considered in pairs. This approach to analysis was of benefit not only because it allowed clear identification of those predictors which were associated with each other but because women with missing data on any variable included in a set of comparative models were necessarily excluded, and so minimising the number of variables included in any one set of models reduced the number of exclusions and maximised power.

Cox's proportional hazards models were used to test the associations between predictor variables and hysterectomy. In the paired analyses three models were run, each predictor was first entered into a model individually and in a third model both predictors were included in the same model. It was ensured that all three models were comparable by excluding women from all three models who had missing data on either one of the two predictor variables or hysterectomy status. Likelihood ratio tests were used to compare the model with both predictors included to the models in which only one of the predictors was included. Tests for interaction between the two predictor variables were also performed using likelihood ratio tests.

This was repeated for each plausible pairing of predictors as discussed above and defined in the objectives (i.e. education and parity; education and BMI at age 26 years; education and age at menarche; age at menarche and BMI at age 26 years; parity and BMI at age 26 years; parity and BMI at age 43 years; parity and BMI at age 53 years). As the association between educational level and hysterectomy attenuated with age and was only significant up to age 44 years models in which educational level was included were run with follow-up only to age 44 years. In models in which BMI at ages 43 and 53 years were included, hysterectomies performed before age 43 and 53 years, respectively, were excluded. In all other models the standard survival model described in chapter 3 (i.e. with follow-up in months since age at menarche to age 57 years) was used. Due to the necessary exclusions when using BMI at ages 43 and 53 years most models in which a measure of BMI in adulthood was required included BMI at age 26 years as this BMI measurement was at an age before any hysterectomies occurred in the NSHD.

In a final model all four main predictors i.e. educational level, age at menarche, parity at age 30 years and BMI at age 26 years were adjusted for in the same model. This model was compared to models in which each one of the predictors was in turn excluded using likelihood ratio tests. As this model included education follow-up was only to age 44 years. In these models women who had missing data on hysterectomy status or any one of the four predictor variables were excluded to ensure comparability of models.

7.7 Results

The size of the association between education and hysterectomy up to age 44 years increased after adjustment for age at menarche, table 7.1. Conversely adjustment for parity and for BMI at age 26 years reduced the size of the point estimates of effect. Despite these attenuations education remained significantly associated with hysterectomy rates after each adjustment and, women with below secondary education still had rates of hysterectomy up to age 44 years over 6 times higher than those women with a degree or higher. These results suggest that age at menarche negatively confounded the association between education and hysterectomy. They also suggest that the association between education and hysterectomy was partially confounded or mediated by parity and BMI at age 26 years but that there was a strong association between education and hysterectomy in earlier adulthood which was independent of these other predictors.

The associations between age at menarche, BMI at 26 years and hysterectomy were not affected by adjustment for education. The size of the association between parity and hysterectomy attenuated after adjustment for educational level, although the association still remained statistically significant. Women who had 3 or more children at age 30 years still had rates of hysterectomy over twice as high as women who had no children by this age. The lack of attenuation of effect of age at menarche suggests that the association between age at menarche and hysterectomy is independent of education. Similarly, the lack of attenuation of effect of BMI at age 26 years after adjustment for education suggests that the association between BMI in adulthood and hysterectomy is not confounded by education. That both the effect of parity and of education attenuated after mutual adjustment suggests that there was a slight overlap between the pathways on which these two predictors operated and that one predictor may have partially confounded or mediated the association between the other predictor and hysterectomy. However, as the attenuations were only small and both predictors remained significantly associated with hysterectomy this overlapping pathway was not the main one on which either predictor was operating.

Neither the association between age at menarche and hysterectomy or between parity and hysterectomy was affected greatly by adjustment for BMI at age 26 years, table 7.2. Likewise, the association between BMI at age 26 years and hysterectomy was not altered markedly by adjustment for parity or age at menarche and the associations between BMI at ages 43 and 53 years were not affected by adjustment for parity. Adjustment for BMI at ages 43 and at 53 years slightly altered the size of the association between parity and hysterectomy although parity remained significantly associated with hysterectomy after adjustment for BMI at age 43 years. The model including BMI at age 53 years did not accurately reflect the association between parity and hysterectomy because many women were excluded from this model as their hysterectomies occurred before age 53 years and so the results from this model were not useful. These results suggest that the association between age at menarche and hysterectomy was independent of adult body weight, that the association between body weight and hysterectomy was independent of parity and the association between parity and hysterectomy was independent of body weight i.e. none of these three predictors were confounded or mediated by either of the other two predictors.

There was no evidence of significant interaction between any of the pairs of predictors examined (results not shown).

When the associations between the four main predictors and hysterectomy were all mutually adjusted for each other the association between age at menarche and hysterectomy was not greatly altered whereas the size of the point estimates of effect for education, parity and BMI at age 26 years attenuated, table 7.3. Despite these attenuations, parity remained significantly associated with hysterectomy, the association between education overall and hysterectomy was still on the borderline of significance and having below secondary education remained significantly associated with elevated rates of hysterectomy. The association between BMI at age 26 years and hysterectomy was not significant even in unadjusted models. This was probably due to the reduction in sample size with the exclusion of women with missing data on any one of the four predictors from this final set of models. These results confirm the findings from the analyses of pairs of predictors and suggest that all four predictors act largely independently of each other to influence hysterectomy risk.

7.8 Discussion

7.8.1 Main findings

The four main predictors of hysterectomy in the NSHD identified in this thesis (i.e. age at menarche, parity, educational level and body weight in adulthood) appeared to act largely independently of each other i.e. no predictor fully confounded the association between another predictor and hysterectomy and all acted on different pathways to influence risk of hysterectomy. A framework showing the four main predictors and the pathways on which they operated to influence hysterectomy risk, a version of figure 7.1 modified in light of this chapter's findings, is shown in figure 7.3.

7.8.2 Comparison with other studies

How the results on associations between each individual predictor identified and hysterectomy compare to the findings from other studies which have examined similar associations have been described in the discussion sections of the previous three chapters. No other study has examined the inter-relationship between different predictors of hysterectomy to the same level as achieved in this thesis.

In those studies which examined the independence of the association between age at menarche and hysterectomy from other factors it was found as in this study that age at menarche was associated with hysterectomy independently of other factors including parity, education, other indicators of adult SEP, BMI, age, smoking and religion.[125;167]

The independence of the association between parity and hysterectomy varies between studies. Some have found, as in this study, that there is an effect of parity which is independent of other predictors including in one study[125] age at menarche, education, BMI, smoking and religion and, in another study indicators of adult SEP.[1] However, in other studies parity was not independently associated with hysterectomy and the association was explained by other predictors including education and adult weight.[128;165;167]

In the majority of studies which have examined it, the association between body weight in adulthood and hysterectomy risk, as in this study, has been found to be independent of other predictors including parity, education, age at menarche and marital status.[126;154;165] However, this is not fully consistent across all studies, as one[125] found no association between BMI and hysterectomy independent of age at menarche, parity and education, although this study was cross-sectional so is not fully comparable with the findings in this thesis.

Education, like age at menarche and body weight has also been consistently found to act independently of other predictors.[125;126;128;137]

7.8.3 Explanation of findings

7.8.3.1 Age at menarche

The maintenance of the inverse association between age at menarche and hysterectomy after adjustment for factors which were identified as most likely to mediate or confound the association suggests that there probably is a direct effect of age at menarche on hysterectomy risk. The independence of this association from other predictors together with the evidence discussed in chapter 6, specifically the variation in association by reason for hysterectomy, and the consistency of this association across studies implicates the presence of a biological pathway acting between age at menarche and hysterectomy, see figure 7.3. As discussed in chapter 6, age at menarche influences length and possibly intensity of exposure to oestrogen across life whereby women who had earlier menarche will have had greater exposure to oestrogen and so increased risk of developing oestrogen dependent gynaecological conditions, some of which are common reasons for hysterectomy e.g. fibroids. Another potential explanation of this association not previously considered is shared genetic risk factors, see figure 7.4, which shows other potential pathways to hysterectomy. It is well established that age at menarche is influenced by genetic factors and has a high level of heritability.[286;287] The oestrogen receptor α gene has been identified as one gene which could influence age at menarche.[288;289] Some polymorphisms of this gene have also been identified as potential predictors of some gynaecological conditions including endometrial cancer[290] and endometriosis[291] and also hysterectomy.[170] It is therefore possible either that age at menarche mediates the association between genetic factors and hysterectomy or that the association between age at menarche and hysterectomy is confounded by genetic factors, investigating this further would be one possible area for future research.

7.8.3.2 Parity

The independence of the positive association between parity and hysterectomy from other factors which could have confounded or mediated the association, i.e. body weight and education, suggests that there is a direct influence of parity on hysterectomy risk.

Inconsistent findings between studies of a particular association are more likely where the pathways underlying the association act on supply and demand factors rather than aetiological pathways. This is because there is more potential for supply and demand factors to be affected by cultural and temporal factors which vary between studies than there is for medical need to be affected by these factors. The inconsistency between studies which have examined the independence of the association between parity and hysterectomy along with the evidence described in chapter 6 and this chapter i.e. the lack of variation in association by reason for hysterectomy and the finding of an association independent of other reproductive characteristics, BMI and education in the NSHD implies that parity acts to influence hysterectomy via its influence on supply and demand factors, figure 7.3. This suggests that the loss of fertility, a consequence of hysterectomy for women who undergo the procedure pre-menopause, is an important consideration and influences women's treatment choices and also possibly the doctor's decision to offer a hysterectomy dependent on their parity.

7.8.3.3 Educational level

The independence of the association between education and hysterectomy up to age 44 years from other predictors of hysterectomy in the NSHD suggests that this factor also had a direct influence on hysterectomy risk and was not mediated by body weight or parity. There was some evidence that the association between education and hysterectomy was negatively confounded by age at menarche and so after appropriate adjustment the association was even larger than originally found. The independence of the association between education and hysterectomy from other factors and, the lack of plausible mechanisms by which education would directly influence an aetiological pathway to medical need for hysterectomy implies that the main pathway on which education operates is via supply and demand factors, figure 7.3. As discussed in chapter 4, there are a number of ways in which education could directly influence supply and demand factors including the ability to engage in the decision making process similar to that shown in figure 3.3.

The suggestion that there may be some variation in the association between education and hysterectomy by reason, as described in chapter 4, suggests that other pathways may also be operating between education and hysterectomy. There are likely to be other factors, such as health-related behaviours e.g. sexual behaviour, smoking and exercise not shown in figure 7.3 but included in figure 7.4 which mediated or confounded the association between education and medical need for hysterectomy.

A further possibility not previously discussed is that an association between education and hysterectomy could exist because of an association with cognitive function in early life, as shown in figure 7.4. There is a growing research interest in the role of cognitive function in early life as a predictor of adult health.[292;293] While the focus of much of this research has been on the association between childhood cognitive function and mortality in adulthood, other health outcomes have been examined. It has been consistently shown that lower childhood cognitive ability is associated with poorer health and mortality outcomes in adulthood.[293] As there is a strong association between indicators of childhood SEP and cognitive function it was initially thought that the associations may be explained by SEP but there is now evidence that the association between childhood cognition and adult health is maintained after adjustment for childhood SEP. This has led some researchers to suggest that socioeconomic differentials in health may be at least partially explained by childhood cognitive function.[294;295] Not only is childhood cognitive function strongly associated with educational attainment but it is also possible that it predicts hysterectomy risk whereby it could confound the association between education and hysterectomy. While no study to date has examined the association between cognitive function and hysterectomy or gynaecological disorders, studies of a related outcome, timing of menopause, suggest that this is predicted by childhood cognitive function, with women who had lower cognitive function in childhood found to reach menopause earlier in the NSHD and other cohorts.[296;297] It is possible that many of the proposed explanations of the association between childhood cognitive function and timing of menopause could also explain an association between cognitive function and development of gynaecological disorders and so medical need for hysterectomy. These include common genetic factors, shown in figure 7.4, shared early environmental risk factors and exposure to endogenous hormones in early life including oestrogen of which childhood cognitive function could be a marker of and which the development of gynaecological disorders could be influenced by. Dependent on the findings from tests of the association between cognitive function and hysterectomy it is possible either that cognitive function confounds the association between education and hysterectomy or that any association between cognitive function and hysterectomy could be mediated or confounded by education. This is an area for future research which may lead to the identification of a further important predictor of hysterectomy risk and elucidate the reasons for finding an association between education and hysterectomy. It is also possible that this area of research could help identify whether hysterectomy and early onset of natural menopause are components of the same phenomenon, which is suggested by the fact that they may be predicted by the same set of risk factors.

7.8.3.4 Body weight

The association between BMI in adulthood and subsequent hysterectomy was found to be independent of age at menarche, education and parity, figure 7.3. It had been proposed in chapter 5 that the most likely explanation of the n-shaped association between BMI in early adulthood and hysterectomy was an association between BMI and one or more other predictor of hysterectomy, the most likely of which was parity. This makes the finding of an association independent of parity surprising and suggests that explanations not previously considered must be responsible for the existence of associations with BMI at different ages in adulthood. While the associations found could still be partially explained by the influence of body weight on the development of gynaecological disorders, possibly through the link between body weight and oestrogen exposure, and also due to some effect of suffering from gynaecological disorders on body weight neither of these explanations are fully consistent with the finding of an n-shaped association between BMI in early adulthood and hysterectomy or the lack of variation in association by reason for hysterectomy.

One possibility, shown in figure 7.4, is that the association is confounded by health-related behaviours and this would need to be investigated further. Another possibility also shown in figure 7.4 is that, like age at menarche, body weight shares common genetic risk factors with the development of gynaecological disorders and hysterectomy risk - there is evidence that BMI is also associated with the oestrogen receptor α gene.[298] In addition to the possible existence of a pathway between body weight in adulthood and medical need for hysterectomy, it may be that body weight is somehow associated with supply and demand factors, although how is not clear. While obesity may have been a contraindication for hysterectomy and this could have changed with time this is not consistent with the finding that the women who were obese at age 26 years not only had lower hysterectomy rates at earlier ages but across the whole period of follow-up. An association between body weight and supply and demand factors would thus require further investigation.

While the associations between BMI across adulthood and hysterectomy could be real it is also possible that they are an artefact of the characteristics of the cohort. Very few women were obese in early adulthood in the NSHD and so there may be other characteristics of this select group which meant they were at lower risk of hysterectomy. In other cohorts where obesity in adolescence and early adulthood is not so unusual the same shape of association between BMI in early adulthood and hysterectomy may not be found. This would need to be explored further using data from other cohorts born at different times which have more variability in BMI at earlier ages.

7.8.3.5 Alternative explanations

In interpreting the findings of this chapter it is important to consider not only the possibility that these are real effects which have been detected but also that the results were due to chance, bias, confounding or reverse causality.

Given the prospective nature of the study and the steps taken in analyses to ensure that each predictor under investigation came in time before the outcome, for all but weight where it was ensured that the measures used came in time before hysterectomy but which may indicate the presence of pre-existing gynaecological disorders, the possibility that the results can be explained by reverse causality can be discounted.

Examination of 95% confidence intervals and p-values from significance tests provide an indication of how likely it is that the results found were due to chance. That the four main predictors were found to be associated with hysterectomy at a statistical significance level of less than 5% suggests that the results are unlikely to be due to chance. More likely is that some other real effects have gone undetected because of the limited statistical power of analyses whereby the possibility that they were due to chance could not be ruled out.

Bias would not be expected to be a major explanation of the findings in this thesis. The cohort were not selected on the basis of their hysterectomy status or any one of the main predictors and most data were collected prospectively whereby selection and recall bias are unlikely. Further, data on the variables included in analyses were not collected specifically for the purposes of this one set of analyses and questions of relevance were framed within much larger questionnaires and, information on predictor variables was collected in time before information on hysterectomy status whereby there is no way that study participants could be aware of the associations under investigation in this thesis and differentially report their exposure status dependent on their hysterectomy status. While selective loss to follow-up could have introduced bias this would not be expected to greatly affect the findings of these analyses and, in comparisons of the relevant characteristics of the women in the NSHD cohort excluded and included there were few significant differences in the distribution of the predictor variables, see the discussion sections of the previous three chapters.

Residual confounding is the most likely alternative explanation of the findings in this chapter. However, by considering the inter-relationship between the different main predictors of hysterectomy identified in the NSHD the possibility that the results are solely due to confounding seems unlikely. As discussed in the explanation section above and as shown in figure 7.4 there are a number of other factors which could confound, modify or mediate the associations investigated in this thesis and these would require further investigation in future analyses.

7.8.4 Limitations

The limitations of analyses examining individual associations between predictors and hysterectomy were described in the previous three chapters and so are not repeated.

To ensure the analyses in this chapter had maximum power, especially given women were necessarily excluded if they had missing data on either one of the two predictors under consideration, it was necessary to group all hysterectomies together. There may have been important variations in some associations by reason for hysterectomy but a larger dataset would be required to investigate these.

In order to keep the framework of predictors of hysterectomy as simple as possible some factors which it may have been important to consider were not included. The indicators of SEP in childhood, father's occupational class and maternal education, were associated with hysterectomy in unadjusted analyses. Although these associations appeared, from analyses described in chapter 4, to be fully explained by education it is possible that they should be shown in the framework because they are mediated rather than confounded by education. This is not a major limitation as the association between indicators of childhood SEP and hysterectomy was not even partially independent of education and so there was no reason to try and identify further confounders or mediators of the association.

The approach to the adjusted analyses used was simple and while this did ensure maximum power and ease of identification of the predictors which were not acting fully independently of each other these models may not have captured the complexity of the associations, especially the association between body weight and hysterectomy or the attenuation in the effect of education over time. Despite this, it has been possible using these analyses to move further towards an understanding of the different ways in which the predictors of hysterectomy identified act to influence hysterectomy risk and it is important to establish in simple analyses what associations and pathways are likely to be operating before moving on to more complex analyses.

The potential limitations of bias and confounding were discussed in section 7.8.3.5.

7.8.5 Strengths

Assessing the independence of predictors of hysterectomy from each other provides insight into the pathways on which the predictors identified were most likely to be operating. Few studies have successfully done this previously despite its value.

This study has the important strength of being a nationally representative cohort. Further, the availability of a range of prospectively collected measures from across life has allowed a more thorough investigation of the inter-relationship between different predictors than has been achieved previously.

7.8.6 Conclusions, implications and future work

In the last four chapters, a number of predictors of hysterectomy in the NSHD have been identified and through a series of analyses it has been possible to identify the most likely pathways on which these factors act. Although potential predictors from across life were examined there was no evidence of a direct effect on hysterectomy risk of any factors before adolescence although all four main predictors identified, i.e. age at menarche, parity, education and body weight in adulthood, are themselves influenced by factors in early life.

Given the complex way in which hysterectomy risk is determined and the variation in the contribution of different factors over time it cannot be expected that if any one of these four factors was modified hysterectomy risk for women would necessarily be reduced. The benefit of the analyses in these four chapters is to help improve understanding of the factors which do predict hysterectomy risk. The presence of associations which are most likely explained by biological/aetiological pathways i.e. the association between age at menarche and hysterectomy suggests that risk of hysterectomy is determined to some extent by medical need for the procedure rather than solely by supply and demand factors. Even where predictors act on supply and demand factors this does not necessarily imply that women are receiving hysterectomy without medical need but, highlights the considerations which are important for women and their doctor's when deciding whether to undergo hysterectomy i.e. parity. The independence of the association between education and hysterectomy from other factors does suggest that women may receive differential treatment especially at younger ages dependent on their educational level which could be of concern. Further research is necessary to examine whether this does lead to women of lower educational level receiving more hysterectomies at young ages despite having no greater medical need and, to examine whether it is patient's demand or doctor's supply factors which explain this association. It is hard to fully understand the implications of the association between body weight and hysterectomy as it is still not clear whether a pathway via medical need or supply and demand factors is operating and further research to examine whether this association is found in other groups of women is required.

As age at menarche, parity, BMI and educational level were all associated with hysterectomy, secular declines in age at menarche over the course of the last two centuries,[299-303] changes in patterns of childbearing,[304] increasing levels of overweight and obesity[200;201] and changes in educational level attained by females[305] could all have influenced changes in the rates of hysterectomy over time. It may be expected that reductions in the average age at menarche and increases in overweight and obesity among women in recent years will have resulted in higher rates of hysterectomy in younger populations although this may be counteracted by the higher educational levels attained by more women. As more women delay childbearing to a later age there may be reductions in hysterectomies performed at young ages and more demand for alternative treatments which preserve fertility. As there are socioeconomic differentials in the changes in childbearing which have occurred over time with women of higher SEP having become more likely to delay childbearing than women of lower SEP, even greater socioeconomic differentials in hysterectomy may have developed in cohorts younger than the NSHD.

This thesis has examined some of the main potential predictors of hysterectomy. Those predictors which could have been acting across life and were most suited to study using data from the NSHD were selected as the focus of analysis. As alluded to in explaining the associations found above it is possible that there are other important predictors not considered in this thesis which could confound the associations found, provide further elucidation of the pathways between the predictors identified and hysterectomy and inform our overall understanding of the prediction of hysterectomy risk. As shown in figure 7.4, childhood cognition, genetic factors, health-related behaviours, family history of hysterectomy and health care utilisation are all potential predictors of hysterectomy and are areas where further research could be pursued. The justification for considering genetic factors, childhood cognition and health-related behaviours were provided in explaining the associations already found in the NSHD above. Health care utilisation is another important area for future research as the way in which women utilise health care could affect their risk of hysterectomy. This is particularly relevant when using a life course approach as it is possible that the way women interpret and manage their gynaecological symptoms, their timing of seeking help for medical care in relation to the timing of onset of symptoms and the severity of symptoms, their trust in the medical care system and wish to consider alternative treatment choices will be influenced by experiences from early life onwards and even possibly by intergenerational factors, such as their relatives' experience of similar symptoms and treatments (hence the inclusion of family history in figure 7.4, although this could also represent shared genetic risk).

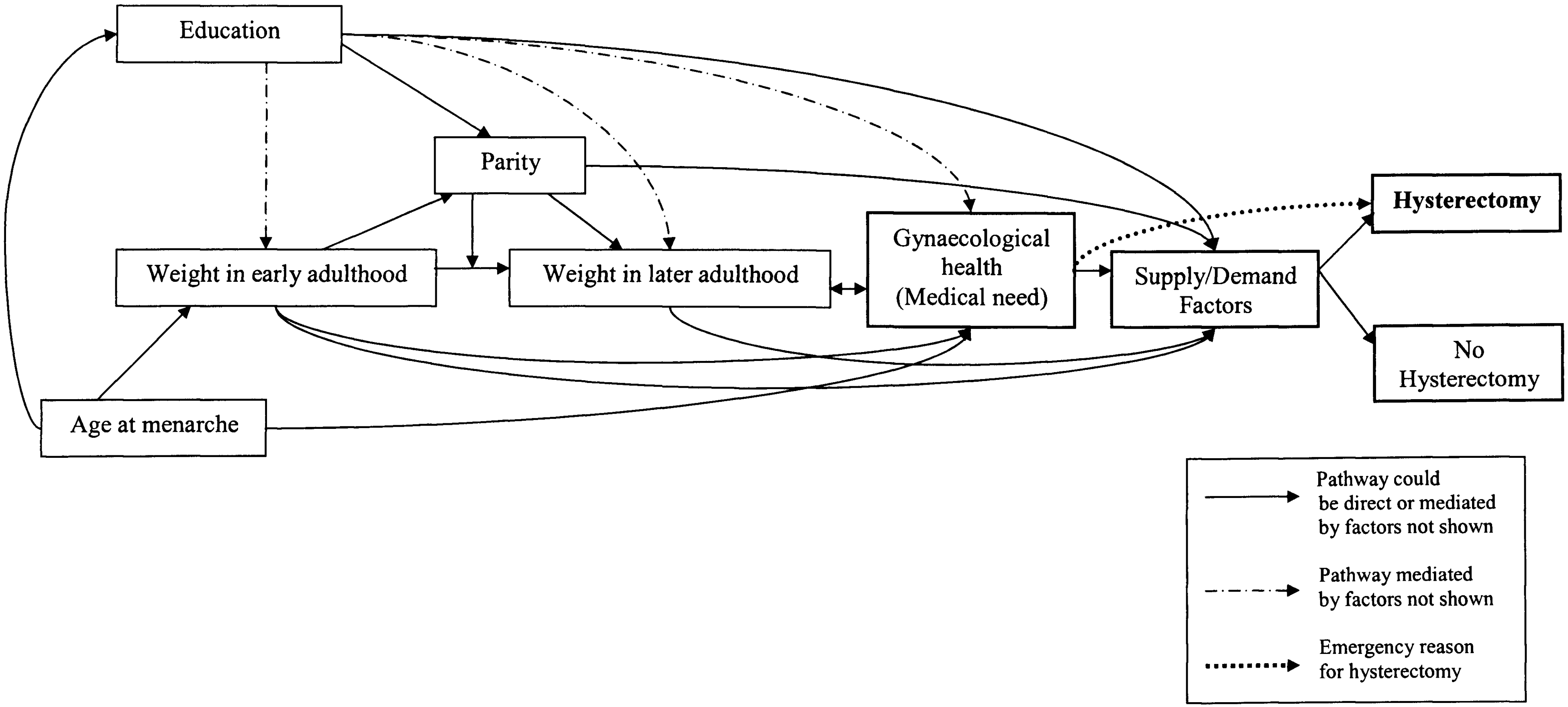
Another potential area for future research would be to consider whether gynaecological conditions are associated with the same factors which predict hysterectomy risk. However, this is methodologically challenging given gynaecological disorders are not as easily detected and reported within populations as hysterectomy. It would however provide a clearer indication of the extent to which hysterectomy is determined by medical need.

Comparing the associations found in the NSHD with associations in other birth cohorts would also be of benefit given it is not clear how generalisable the results from this thesis are to women born at different times. This is especially important given there was evidence that the association between SEP and hysterectomy varied by birth cohort suggesting that there could be variation in other associations by birth cohort.

Future analyses could utilise the findings from these analyses and any analyses identifying other potential predictors to perform more sophisticated analyses for example, structural equation modelling. These more advanced models may provide an even greater understanding of the pathways to hysterectomy however, such analyses are better conducted once more basic analyses such as have been used in this thesis have identified suitable variables for inclusion in the models.

Having defined some of the main predictors of hysterectomy in the NSHD it is necessary to use this information to inform the selection of covariates for inclusion in analyses of the health consequences of hysterectomy. If factors which predict hysterectomy also predict the health consequence under study they may confound the association between hysterectomy and the health outcome and so need to be included in analyses. Failure to do so may lead to inappropriate conclusions about the health consequences of hysterectomy being made. The health consequences of hysterectomy are investigated in the following section of the thesis.

Figure 7.1: Framework of the potential relationships between the different predictors of hysterectomy in the NSHD

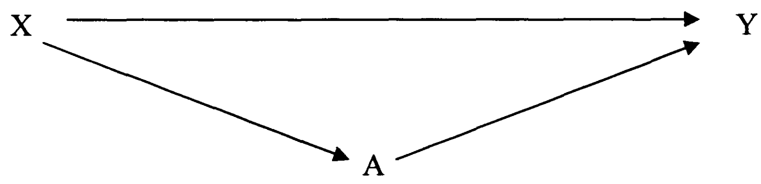


Please note: Only those potential relationships between the different factors in the figure relevant to the prediction of hysterectomy risk are shown

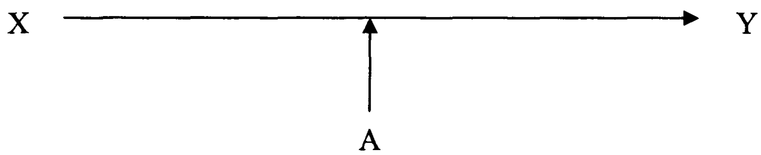
Figure 7.2: Three possible scenarios representing the relationship between X (exposure), Y (outcome), and a third variable A

Taken from Singh-Manoux, 2005[273]

(1) A as a mediator



(2) A as a moderator



(3) A as a confounder

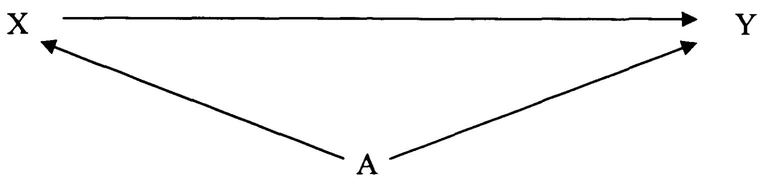
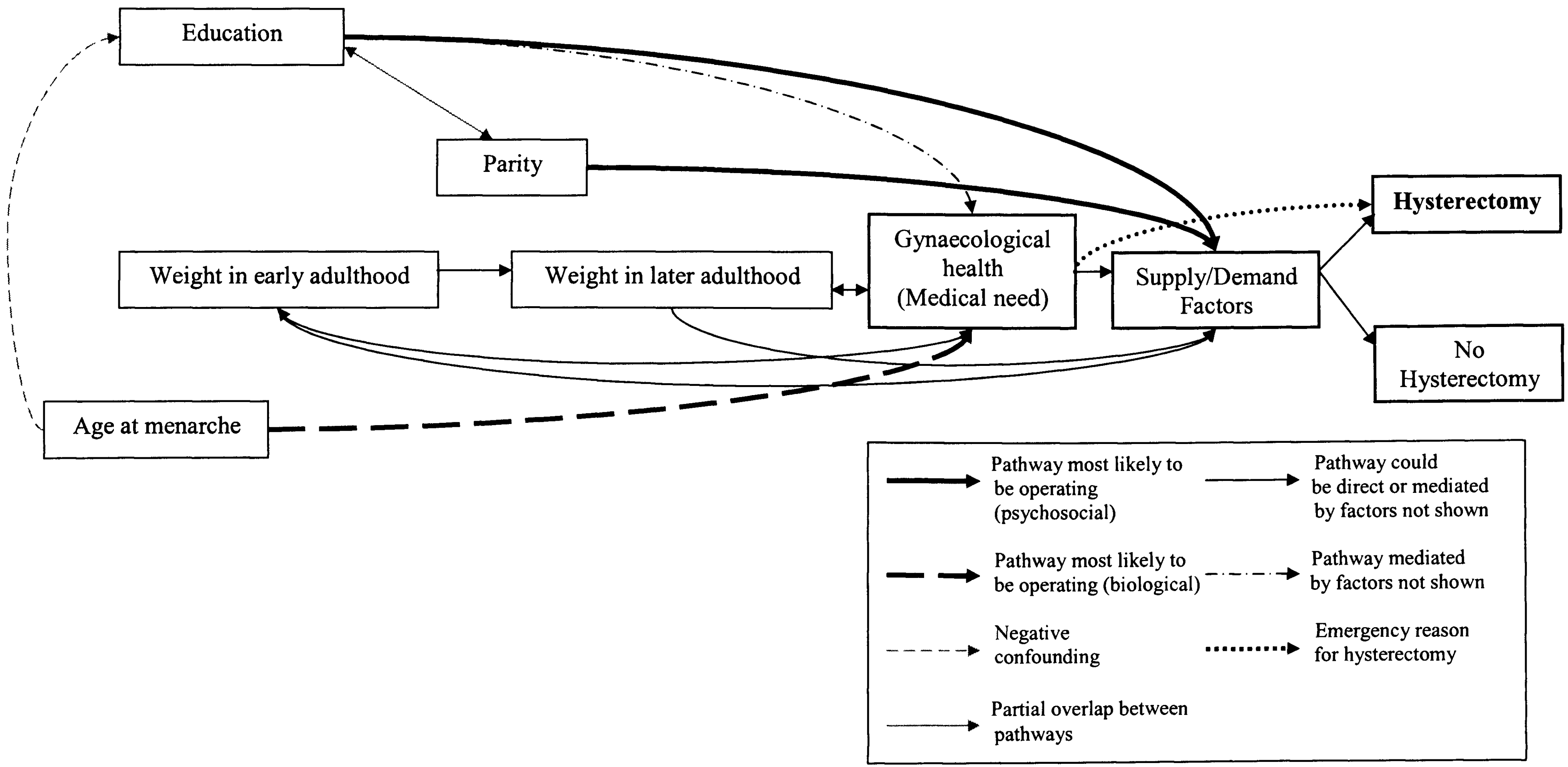
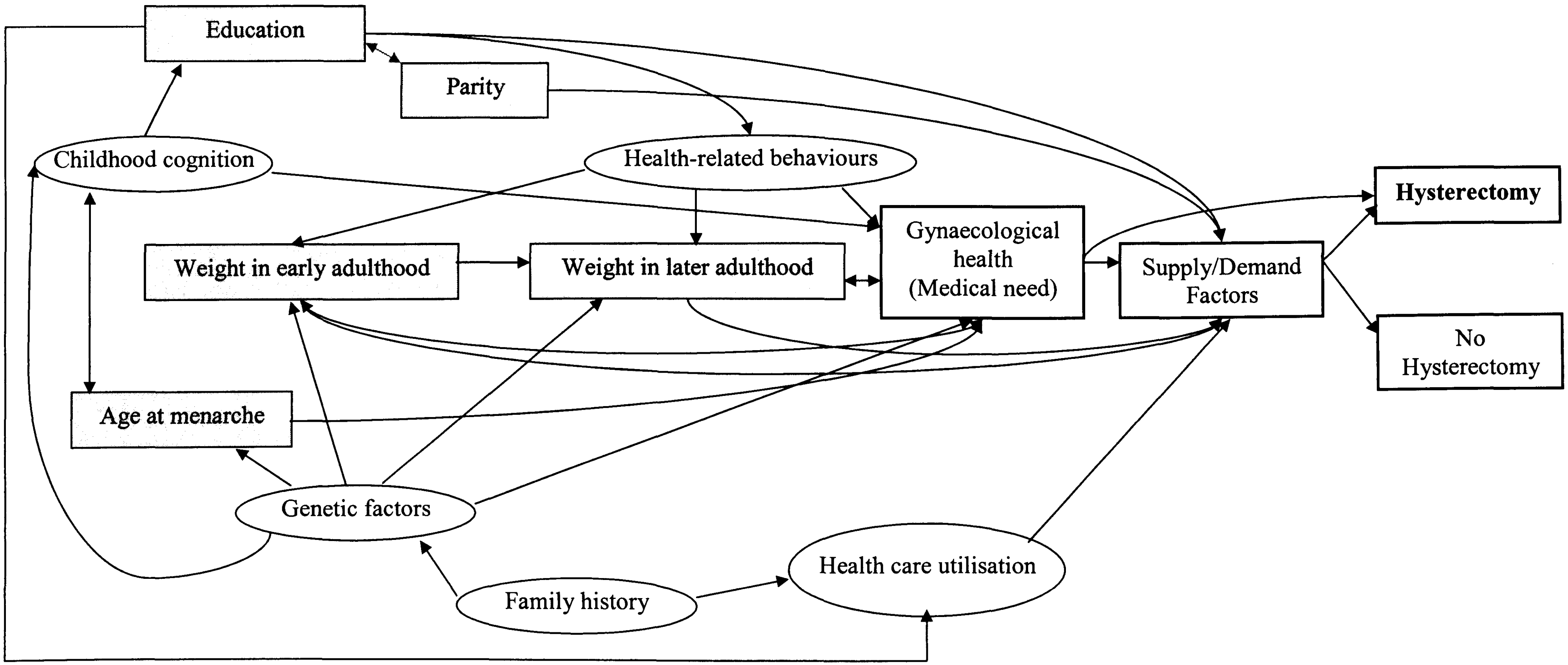


Figure 7.3: Framework of the relationship between the different predictors of hysterectomy identified in the NSHD



Please note: Only those relationships between the different factors in the figure relevant to the prediction of hysterectomy risk are shown

Figure 7.4: Framework showing other potential predictors of hysterectomy and so areas of further possible research



Please note: Only those relationships between the different factors in the figure relevant to the prediction of hysterectomy risk are shown

Table 7.1: Survival analyses of the association between predictor variables and hysterectomy adjusted for a second predictor variable in the NSHD (Follow-up to age 44 years)

Predictors of hysterectomy	N	Unadjusted Hazard Ratio for hysterectomy (95% CI)	Hazard Ratio for hysterectomy (95% CI) adjusted for other variable in pair
Educational level	1348		
Degree or higher		1.00	1.00
Advanced secondary		3.06 (0.72, 12.92)	3.20 (0.76, 13.51)
Ordinary secondary		3.90 (0.94, 16.22)	4.03 (0.97, 16.76)
Below secondary		6.17 (1.45, 26.32)	6.53 (1.53, 27.89)
None		4.35 (1.06, 17.81)	4.63 (1.13, 18.96)
p-value		*0.02*	*0.01*
Age at menarche			
per 1 year increase		0.85 (0.74, 0.98)	0.84 (0.73, 0.96)
p-value		*0.02*	*0.01*
Educational level	1642		
Degree or higher		1.00	1.00
Advanced secondary		3.76 (0.90, 15.73)	3.40 (0.81, 14.27)
Ordinary secondary		4.39 (1.06, 18.18)	3.87 (0.93, 16.06)
Below secondary		7.71 (1.83, 32.53)	6.48 (1.53, 27.51)
None		5.78 (1.42, 23.51)	4.72 (1.15, 19.32)
p-value		*0.001*	*0.009*
Parity (No. of children) 0		1.00	1.00
1		1.92 (1.07, 3.44)	1.77 (0.99, 3.17)
2		2.01 (1.19, 3.40)	1.74 (1.03, 2.96)
≥3		2.77 (1.59, 4.82)	2.34 (1.33, 4.12)
p-value		*0.002*	*0.02*
Educational level	1483		
Degree or higher		1.00	1.00
Advanced secondary		3.36 (0.80, 14.12)	3.33 (0.79, 13.99)
Ordinary secondary		4.14 (1.00, 17.18)	4.02 (0.97, 16.71)
Below secondary		7.51 (1.77, 31.86)	7.37 (1.74, 31.26)
None		4.91 (1.20, 20.07)	4.72 (1.15, 19.34)
p-value		*0.003*	*0.004*
BMI (kg/m^2) at age 26 years			
per 1 unit increase in BMI		1.15 (1.03, 1.29)	1.14 (1.02, 1.27)
per 1 unit increase in BMI^2		0.99 (0.98, 1.00)	0.99 (0.98, 1.00)
p-value		*0.02*	*0.04*

Table 7.2: Survival analyses of the association between predictor variables and hysterectomy adjusted for a second predictor variable in the NSHD (Follow-up to age 57 years)

Predictors of hysterectomy	N	Unadjusted Hazard Ratio for hysterectomy (95% CI)	Hazard Ratio for hysterectomy (95% CI) adjusted for other variable in pair
Age at menarche	1247		
per 1 year increase		0.85 (0.77, 0.94)	0.86 (0.78, 0.95)
p-value		*0.001*	*0.003*
BMI (kg/m²) at age 26 years			
per 1 unit increase in BMI		1.14 (1.05, 1.24)	1.13 (1.03, 1.23)
per 1 unit increase in BMI²		0.99 (0.98, 1.00)	0.99 (0.98, 1.00)
p-value		*0.001*	*0.003*
	1507		
Parity (No. of children) 0		1.00	1.00
1		1.84 (1.22, 2.76)	1.84 (1.22, 2.76)
2		1.80 (1.25, 2.59)	1.76 (1.22, 2.53)
≥3		2.66 (1.80, 3.91)	2.61 (1.77, 3.84)
p-value		*<0.0001*	*<0.0001*
BMI (kg/m²) at age 26 years			
per 1 unit increase in BMI		1.13 (1.05, 1.22)	1.12 (1.04, 1.21)
per 1 unit increase in BMI²		0.99 (0.98, 1.00)	0.99 (0.98, 1.00)
p-value		*0.001*	*0.002*
Women excluded from analyses if age at hysterectomy ≤43 years			
	1438		
Parity (No. of children) 0		1.00	1.00
1		1.66 (1.00, 2.74)	1.68 (1.01, 2.77)
2		1.55 (0.99, 2.42)	1.52 (0.97, 2.39)
≥3		2.39 (1.48, 3.85)	2.32 (1.44, 3.74)
p-value		*0.003*	*0.005*
BMI (kg/m²) at age 43 years			
per 1 unit increase in BMI		1.14 (1.05, 1.23)	1.13 (1.05, 1.22)
per 1 unit increase in BMI²		0.995 (0.991, 0.999)	0.995 (0.991, 0.999)
p-value		*0.001*	*0.002*
Women excluded from analyses if age at hysterectomy ≤53 years			
	1169		
Parity (No. of children) 0		1.00	1.00
1		0.59 (0.11, 3.21)	0.56 (0.10, 3.06)
2		1.30 (0.41, 4.14)	1.25 (0.39, 4.00)
≥3		1.10 (0.25, 4.90)	1.00 (0.22, 4.50)
p-value		*0.74*	*0.73*
BMI (kg/m²) at age 53 years			
per 1 unit increase in BMI		1.07 (1.00, 1.13)	1.07 (1.00, 1.14)
p-value		*0.04*	*0.06*

Table 7.3: Survival analyses of the association between predictor variables and hysterectomy adjusted for other predictor variables in the NSHD (N=1,197) (Follow-up to age 44 years)

Predictors of hysterectomy	Unadjusted Hazard Ratio for hysterectomy (95% CI)	Hazard Ratio for hysterectomy (95% CI) adjusted for all other variables
Educational level		
Degree or higher	1.00	1.00
Advanced secondary	2.69 (0.63, 11.40)	2.66 (0.63, 11.32)
Ordinary secondary	3.26 (0.78, 13.59)	3.07 (0.73, 12.87)
Below secondary	5.69 (1.33, 24.36)	5.34 (1.24, 23.01)
None	3.55 (0.86, 14.59)	3.21 (0.77, 13.36)
p-value	*0.03*	*0.06*
Age at menarche		
per 1 year increase	0.84 (0.72, 0.97)	0.83 (0.72, 0.97)
p-value	*0.02*	*0.02*
Parity (No. of children) 0	1.00	1.00
1	2.08 (1.05, 4.13)	1.98 (1.00, 3.94)
2	1.85 (0.99, 3.46)	1.66 (0.88, 3.12)
≥3	2.78 (1.44, 5.36)	2.47 (1.27, 4.81)
p-value	*0.01*	*0.03*
BMI (kg/m^2) at age 26 years		
per 1 unit increase in BMI	1.12 (1.00, 1.25)	1.09 (0.97, 1.22)
per 1 unit increase in BMI^2	0.99 (0.98, 1.00)	0.99 (0.98, 1.00)
p-value	*0.11*	*0.24*

Chapter 8: An introduction to the health consequences of hysterectomy

8.1 Introduction

This, the second major section of the thesis, examines the health consequences of hysterectomy. This chapter reviews the literature on the health consequences of hysterectomy and introduces the health consequences examined in the following three chapters: body weight; musculoskeletal health; and psychological health and self-perceptions of the effect of hysterectomy.

Gathering empirical evidence about the consequences of hysterectomy as well as the predictors is important especially as a comprehensive assessment of the appropriateness of hysterectomy cannot be made unless all costs and benefits of the procedure are fully understood. Health outcomes are one of the main set of factors to be considered in any cost benefit analysis of hysterectomy although, it should be acknowledged that they are not the only consideration, for example, there are also economic costs and benefits of hysterectomy[11;19;306;307] although these will not be discussed.

There is a benefit in studying the consequences of hysterectomy from a life course perspective - the importance of hysterectomy as an event in a woman's life cannot be understood unless the effect of hysterectomy on future health outcomes and risk profiles are known.

The health consequences of hysterectomy are not well defined even though the procedure has been common practice for nearly a century. This is because hysterectomy was introduced long before the rise of evidence-based medicine which demands that the benefits of a procedure are demonstrated to outweigh any costs before it is introduced. As the literature review will show, although many studies have attempted to assess the health consequences of hysterectomy most have a number of limitations and there are many areas where further research is necessary.

The lack of convincing and consistent evidence of associations between hysterectomy and potential health outcomes led McPherson and colleagues to suggest in 2005 that:

'Further rigorous research into the incidental long-term complications of hysterectomy is long overdue and much needed. It is time to abandon shortsightedness in the clinical evaluation of common treatments if we want to avoid their long-term public health costs - both financial and in preventable human suffering.'[308] (p.474)

This was echoed in an editorial in the British Medical Journal by Edozien, also published in 2005, which suggested that,

'More robust evidence on the longer term outcomes of hysterectomy is required, especially for those outcomes that are important to patients'[309] (p.1457)

8.2 Literature review

8.2.1 Introduction

Studies which have examined the health consequences of hysterectomy date back over many years. In 1951 Knutsen[227] examined the consequences of hysterectomy in a group of 118 women. The main outcome of interest was menopausal symptoms but Knutsen also observed mental depression, impaired memory, increased body weight and changes in libido. In the same decade Dalton[225] followed-up 43 women in her general practice who had undergone hysterectomy and examined consequences including marital happiness, satisfaction with the procedure, neurosis and weight gain. These studies are of limited use as they have small sample sizes and lack comparison groups but they demonstrate that the health consequences of hysterectomy have concerned researchers for a long time, making the fact that they are still not well defined surprising.

The main limitation of early studies is that they had inappropriate study designs a problem which has, in more recent years been addressed, as epidemiological methods and statistical techniques have advanced and, with the increased recognition of the need to approach the study of health outcomes systematically. Reviews[8;11;19;46;310;311] of more recent studies have been published and provide useful summaries of this existing research.

Most health consequences of hysterectomy can be considered as short- or long-term, although there is overlap between the two. This thesis focuses on the potential long-term consequences but a brief consideration of short-term effects is made.

8.2.2 Short-term health consequences of hysterectomy

The most serious short-term consequence of hysterectomy is mortality. Mortality rates for the period immediately following hysterectomy vary dependent on the reason for the procedure but in all cases tend to be low.[2;8;173;310;312;313] More common are non-fatal complications - estimated complication rates within the range 25 to 50% have been reported.[8] Although complication rates are high many complications are minor and reversible with rates of major complications reported to range between only 3 and 7%.[2;310;312]

Many short-term complications of hysterectomy are similar to those for other surgical procedures[8] and include: post-operative fever; wound infection; septicaemia; haemorrhage; urinary tract infection; and damage to other organs and structures including, in the case of hysterectomy, the bladder, ureter, urethra and bowel.[8;11;19;57;310-312;314-316] There is evidence to suggest that the risk of such operative complications is not uniform and that some women who undergo hysterectomy are at higher risk than others. McPherson and colleagues[312] found that younger age at procedure, increased parity, fibroids as the reason for hysterectomy, a history of serious illness and having a laparoscopically assisted hysterectomy were all factors associated with increased risk of serious complications within 6 weeks of surgery.

Not all short-term consequences of hysterectomy, despite the focus in many papers and amongst anti-hysterectomy groups, are detrimental, there are also beneficial outcomes. Hysterectomy has been found to immediately and effectively abolish or relieve many of the symptoms which cause women to consult a doctor and be offered a hysterectomy.[11;228;229;310;317] The alleviation of symptoms probably explains the fact that women tend to report satisfaction with the procedure. An American study[317] examined the short-term satisfaction of women with their hysterectomies and found that most women were satisfied. Those women who were dissatisfied were more likely to have been readmitted to hospital within a year of their hysterectomy and not to have benefited from symptom relief. This supports the idea that the reduction in gynaecological and other symptoms following hysterectomy which most women appear to benefit from is one reason why women, in studies which have examined this, are often satisfied with the procedure[19;57;317;318] and report an improvement in their quality of life.[319]

8.2.3 Long-term health consequences of hysterectomy

8.2.3.1 Symptom relief

Relief of symptoms is a consequence of hysterectomy which takes effect immediately, in addition, the same gynaecological symptoms are unlikely to recur for the remainder of a woman's life making it and the patient satisfaction often associated with this, long-term consequences also.[229] In a British study[320] the hospital readmissions of women who underwent hysterectomy for dysfunctional uterine bleeding were compared with those of women who underwent an alternative, less radical treatment (transcervical resection of the endometrium) for the same problem. This found that hysterectomised women were less likely to be readmitted to hospital up to 5 years later for any reason and significantly less likely to be readmitted for gynaecological reasons. A Canadian study[173] found similarly that women who underwent hysterectomy were hospitalised and consulted their doctors about gynaecological problems less often following hysterectomy compared to other women. In this study consultations about other symptoms (e.g. psychological and menopausal) did however, increase and were higher than levels found in the non-hysterectomised comparison group. In an American study[317;319] which followed hysterectomy patients for 2 years post-procedure, there was a reduction in the number of women reporting gynaecological, psychological and other symptoms and an improvement in quality of life and social and physical function when comparing levels of these factors reported pre-procedure with levels post-procedure. There were however, a small group of women (8% of the population), who were more likely to have low incomes and be in therapy at the time of hysterectomy, for whom there was a lack of symptom relief suggesting that the benefits of hysterectomy experienced by a woman may be influenced by social factors and levels of pre-existing comorbidity.

Other long-term potential consequences of hysterectomy discussed in the literature are: mortality; cancer; cardiovascular disease (CVD); hormonal changes; musculoskeletal health; psychological and sexual outcomes; quality of life; bowel and bladder function; and weight change. The literature on body weight has already been reviewed in chapter 5 and so, to avoid repetition this consequence, despite being important, will not be discussed again in this chapter's review.

8.2.3.2 Long-term all-cause mortality

Only two studies[321;322] have examined the association between hysterectomy and long-term mortality. The first of these[321] found no evidence of an association but had limitations the most important of which was that women who had a hysterectomy could have been misclassified as non-hysterectomised. Further, follow-up was only for an average of 5.6 years. In a more recent study, Iversen and colleagues,[322] found no significant association between hysterectomy and subsequent all-cause, CVD or cancer mortality over approximately 20 years of follow-up in a British cohort - most estimates of effect suggested a non-significant reduction in mortality for hysterectomised women when compared with non-hysterectomised women. This study was: unable to adjust for HRT use which could have confounded the association; had a study population who were healthier than the general population; and did not investigate whether there was any difference in outcome dependent on oophorectomy status or reason for hysterectomy.

The lack of an association between hysterectomy and cancer or CVD mortality[322] suggests that there may be no association between hysterectomy and the incidence of these two groups of diseases.

8.2.3.3 Cancer

In a major Finnish study,[323] there was no significant association between hysterectomy and subsequent overall cancer risk. There was evidence to suggest, as would be expected, that with removal of gynaecological organs risk of subsequent gynaecological cancers was reduced. In addition to a reduction in risk of some cancers there was also a slightly increased risk of cancer at other sites (rectum, thyroid and lung). This study was limited by the fact that no distinction was made between women who had a hysterectomy with ovarian preservation and women who had a hysterectomy accompanied by oophorectomy whereby it was not possible to separate the effect attributable to hysterectomy from the effect attributable to oophorectomy. A strength of this study was that it excluded women who had suffered from gynaecological cancer. This is important given women who had hysterectomy for cancer would be at greater risk of developing cancer at other sites than other women and if included could cause the independent effect of hysterectomy on subsequent cancer risk to appear greater than it is.

In addition to the removal of risk of cancer of organs and structures removed during hysterectomy other studies have found that hysterectomy could reduce the subsequent risk of breast cancer[19;324-326] and, even in women whose ovaries were preserved, ovarian cancer.[19;327;328] It has been proposed that a reduction in risk of ovarian cancer in hysterectomised women with ovarian preservation results from a 'healthy screenee' effect whereby women, while having their hysterectomy, undergo a check of their ovaries and have them removed if they are not healthy.[329] However, the reduction in ovarian cancer risk has been found to persist over long periods of follow-up[327-329] and along with other evidence[330] this suggests that a 'healthy screenee' effect is an unlikely explanation. Other proposed explanations include the fact that hysterectomy: compromises blood flow to the ovaries; disrupts hormone levels and/or; interrupts retrograde transportation of carcinogens from the vagina to the ovaries.[327;328]

There appear to be no other studies which have replicated an association between hysterectomy and increased risk of rectal or lung cancer found in the Finnish study[323] suggesting that these may have been chance findings. However, another Finnish study conducted by the same researchers found further evidence of an increased risk of thyroid cancer associated with hysterectomy in the two years post-procedure.[331] Rather than looking for causal mechanisms which could explain this association the authors of this study have suggested that the association between hysterectomy and subsequent thyroid cancer is due to a shared aetiology of thyroid cancer and gynaecological problems.

That hysterectomy, from the existing evidence, appears to be associated with a reduced risk of some cancers and a slightly increased risk of others with no effect found when all cancers are considered together supports the evidence from Iversen and colleagues[322] mortality study. As for the mortality study, studies of the association between hysterectomy and subsequent cancer are often limited by: a failure to separate the effect of hysterectomy from any independent effect of oophorectomy; no consideration of reasons for hysterectomy; and no control for potential confounders.

8.2.3.4 Cardiovascular disease

A number of studies have investigated the association between hysterectomy and CVD outcomes[19;129;156;332] (e.g. myocardial infarction) and/or cardiovascular risk profile[130;142;144;156;159;163;333] (e.g. hypertension, cholesterol levels), including the NSHD,[163] Rancho-Bernardo study[159] and the Women's Health Initiative.[129;142] These studies provide some evidence to suggest that hysterectomy may be associated with CVD outcomes and high-risk profiles however, this is not consistent.

In a Swedish study,[332] hysterectomy was associated with higher risk of myocardial infarction but only amongst women who had undergone the procedure post-menopause with this risk greatest for women who had undergone a hysterectomy for fibroids. In a Finnish study,[156] hysterectomy with ovarian preservation was associated with increased risk of angina-pectoris, myocardial infarction and heart failure but these effects were not significant after adjustment for cardiovascular risk factors. Similarly in a study of the Women's Health Initiative[129] hysterectomy regardless of oophorectomy status was associated with greater risk of fatal and non-fatal cardiovascular events but after adjustment for demographic and cardiovascular risk factors this effect attenuated and was non-significant. These results suggest that women who undergo hysterectomy may be at greater risk of CVD because they have poorer cardiovascular risk profiles rather than because of a direct causal effect of hysterectomy on CVD events. The questions are then whether hysterectomy influences cardiovascular risk profile and what common factors could predict hysterectomy and increased cardiovascular risk.

Some studies[130;144;163;333] have found evidence that hysterectomy even with ovarian preservation is associated with poorer cardiovascular risk profile including the two studies[129;156] detailed above which adjusted for such factors in analyses of CVD outcomes. However, this is not consistent across studies. In the Rancho-Bernardo study[159] women who had undergone an oophorectomy had a poorer CVD risk profile but, women who had undergone a hysterectomy with ovarian preservation had risk profiles similar to women in the comparison group. Likewise in a study by Hsia and colleagues,[142] although hysterectomy with bilateral oophorectomy was an independent predictor of Framingham risk score (which is comprised of factors such as: age, blood pressure, current smoking, total and high density lipoprotein cholesterol and hypertension treated with medication) hysterectomy with ovarian preservation was not. One limitation of the majority of these studies is that they were cross-sectional and so it is not possible to establish the temporal relationship between hysterectomy and CVD risk profile. Further, few studies have adjusted for all appropriate confounders especially HRT use which many women who have a hysterectomy are prescribed[334] and which may, given its own potential long-term influence on CVD risk,[335] confound the association.

While it is possible that hysterectomy even with ovarian preservation could directly influence CVD risk profile and/or subsequent risk of CVD events, possibly through its effect on reductions in oestrogen exposure or through loss of the protective effect of iron loss during menstruation, authors have also proposed that associations between hysterectomy and CVD may have been found because hysterectomy and CVD share common risk factors or because there are similar pathways underlying the development of gynaecological disorders (such as fibroids) and CVD risk factors (such as hypertension and atherosclerosis).[129;130;156;175;332;336;337] However, none of these proposed explanations have been confirmed.

8.2.3.5 Oestrogen exposure

One mechanism which could explain an association between hysterectomy and CVD and some cancers (such as breast) as well as other health outcomes is through hysterectomy's influence on oestrogen exposure. There is strong evidence that the risk of developing many health conditions is influenced by hormonal exposures.[338] For pre-menopausal women who undergo hysterectomy accompanied by oophorectomy, and hence have their main source of endogenous oestrogen removed, an immediate reduction in oestrogen exposure is inevitable. More unexpectedly, pre-menopausal women undergoing hysterectomy whose ovaries are preserved may still be subject to changes in oestrogen exposure if, as has been suggested, hysterectomy affects the preserved ovaries' production of oestrogen and is associated with premature ovarian decline.[8;339]

Premature ovarian failure was proposed as a consequence of hysterectomy as early as the late nineteenth century.[8] A number of studies in the last few decades have attempted to test this proposal in women who have undergone pre-menopausal hysterectomies with ovarian conservation however, the results from these are not fully consistent.

In studies examining the short-term effect of hysterectomy on ovarian function i.e. within a week of surgery there is some evidence that hysterectomy is associated with a reduction in ovarian function as indicated by significant reductions in serum levels of estradiol and progesterone.[340;341] However, this was not found in all studies[342] and in those where it was, at subsequent follow-ups 1 and 6 months after surgery hormone levels were found to be no different from pre-operative levels suggesting any effect of hysterectomy may have been transient.[340;341;343] In studies with longer follow-up, which have more relevance in determining whether any association between hysterectomy and ovarian function is a public health concern, there is evidence to suggest that hysterectomy may have longer-term effects on ovarian function than the short-term studies imply.

A number of studies have found evidence to suggest that hysterectomised women with ovarian conservation suffer ovarian failure, as indicated by timing of the onset of menopausal symptoms or reproductive hormone concentrations in the blood, at a significantly earlier age than women who have not had hysterectomy.[339;344-351] However, other similar studies have found no association between hysterectomy and long-term ovarian function[352-356] or have found that hysterectomised women actually have higher serum oestradiol and lower follicle stimulating hormone (FSH) levels, indicating normal ovarian function, than naturally menopausal women.[157] The results from all these studies do however need to be interpreted with caution as they have limitations. The most important limitation of Siddle and colleagues' study,[339] which was one of the first to examine this association, is that timing of ovarian failure was measured differently in the hysterectomy and the comparison group. While time of ovarian failure in the comparison group was taken to be time of natural menopause (i.e. period cessation), in the hysterectomy group time of ovarian failure was measured as time of onset of menopausal symptoms, which can in women with natural menopause occur years prior to period cessation. Some limitations common to most of the studies include: their small sample sizes (i.e. often < 100 women);[350-353;355;356] a lack of a comparison group;[344;346;352;356] relatively short follow-up;[353] a reliance on retrospective recall of timing of menopause;[339] and lack of adjustment for confounders (e.g. age, smoking, unilateral oophorectomy).[157;339;346;349;352] The last of these limitations is important given there is a possibility that hysterectomised women may be at increased risk of premature ovarian failure regardless of their hysterectomy status.

A recent study[153] has tried to address the limitations of earlier studies using a prospective cohort design. Farquhar and colleagues found that women who underwent hysterectomy with preservation of their ovaries reached menopause (as measured by an increase in FSH levels to > 40 IU/L) 3.7 years earlier than women who had not undergone hysterectomy even after excluding women with elevated FSH levels at baseline and adjustment for baseline FSH levels, BMI and smoking. This provides the most convincing, although not conclusive, evidence to date that there may be an effect of pre-menopausal hysterectomy on timing of ovarian failure. As this study followed-up only 516 women for 5 years they had to extrapolate their results to produce estimates of timing of menopause which may be inaccurate.

It has been proposed that hysterectomy could affect ovarian function and timing of decline in function via an association between hysterectomy and a restriction in blood flow to the ovaries which even if acute could, it has been suggested, lead to a loss of ovarian reserve. This explanation is supported by a study which showed that hysterectomy resulted in an acute reduction in blood flow to the ovaries[357] and another study which showed that in the longer-term women of reproductive age who had undergone hysterectomy had reduced blood flow in their ovarian arteries compared to women who had not undergone gynaecological surgery.[358] Another possible explanation is that some gynaecological disorders which result in hysterectomy could also affect the ovaries and therefore independently influence timing of ovarian failure.[339] Alternatively, the gynaecological disorders which result in hysterectomy, especially menstrual disorders with no underlying pathology, could be the first symptoms of the onset of an early menopause.[153]

8.2.3.6 Musculoskeletal health

Although the association between hysterectomy and endogenous oestrogen exposure is still not clear, if there is a relationship it might be expected that an association between hysterectomy and some components of subsequent musculoskeletal health would be found. Oestrogen exposure is strongly associated with one component of musculoskeletal health, bone mineral density (BMD).[157;359-361] In some studies[362-367] oestrogen exposure has also been found to be associated with other measures of musculoskeletal health - muscle strength and postural balance - although this is not consistent across all studies.[368-375]

Studies of the association between hysterectomy and musculoskeletal health have focussed on bone. Watson and colleagues[376] found that women who had undergone pre-menopausal hysterectomy with ovarian conservation had significantly lower spine and femoral neck BMD than women who had not undergone hysterectomy. However, this study did not adjust for potentially important confounders and may not be generalisable as women who had taken HRT, who were regular smokers or who were heavy consumers of alcohol were excluded. In a case-control study,[377] hysterectomy with or without oophorectomy was associated with significantly increased risk of pelvis fracture after adjustment for BMI, HRT use and smoking status which also suggests hysterectomy may have a negative effect on bone density and postural balance.

Conversely, cross-sectional studies in the UK,[378] Norway,[379] Australia[157] and Sweden[144;380] have found that women who had undergone pre-menopausal hysterectomy had higher BMD than women who had undergone natural menopause suggesting a protective effect of hysterectomy. In Grainge and colleagues' study[378] of a UK population the effect was found even after adjustment for age, years since menopause or hysterectomy, duration of HRT use, height, weight, duration of smoking and family history of fracture and, there were no significant differences in these findings by oophorectomy status or reason for hysterectomy.

In addition to studies which have found either a positive or negative association there are also studies[359;381;382] which have found no association between hysterectomy and bone density. The evidence for an association between hysterectomy and the aspects of musculoskeletal health which have been studied is therefore inconsistent and conflicting.

While most of these studies are well-designed in that they have assessed the effect of hysterectomy independent of oophorectomy and have adjusted for a range of confounders, there are also limitations. One of these is that nearly all studies[157;376;378;379;381;382] were cross-sectional and so they were not able to examine the temporal relationship between hysterectomy and musculoskeletal health. Further, most studies were restricted to the study of bone density despite the fact that hysterectomy could also plausibly influence other components of musculoskeletal health.

If hysterectomy influenced musculoskeletal health through its association with the timing of ovarian failure and a premature reduction in oestrogen exposure it might be expected that hysterectomy would have a negative influence on outcomes such as BMD and muscle strength given a reduction in oestrogen exposure is associated with bone loss[157] and possibly also with declines in other measures of musculoskeletal health such as muscle strength.[383] However, other pathways associated with oestrogen exposure may operate in the opposing direction resulting in hysterectomy having a protective effect. Fibroids and some other reasons for hysterectomy are oestrogen dependent whereby hysterectomy may be a marker of high levels of oestrogen exposure and thus of higher BMD[379] and other measures of good musculoskeletal health. Another possibility is that hysterectomised women have more body fat than naturally menopausal women whereby they have greater protection from fractures if they fall and higher endogenous oestrogen production protecting them from bone loss.[157] However, some studies have found an effect of hysterectomy on BMD even after adjustment for BMI and the evidence that hysterectomised women actually have higher levels of body fat than other women is not consistent or convincing and will be examined in the next chapter.

In addition to pathways associated with oestrogen exposure it is also possible that hysterectomy is associated with subsequent musculoskeletal health for other reasons. While recovering from hysterectomy, women's activity levels may be greatly restricted causing losses in bone and muscle mass which may not be easily reversed once recovery is complete. Another possibility is that there are shared risk factors for hysterectomy and musculoskeletal outcomes. For example, some polymorphisms of the Vitamin D and oestrogen receptor genes have been found to protect against hysterectomy,[162;170] other polymorphisms of these same genes have been found to be associated with musculoskeletal outcomes.[384-386]

8.2.3.7 Incontinence

There is an increasing research interest in health conditions which do not directly cause death but which impact greatly on quality of life and, because of their association with age are expected to become more prevalent in the next few decades as populations across much of the world age. Musculoskeletal health outcomes are one set of such conditions and incontinence another. The risks of both urinary and faecal incontinence are influenced by many factors one of which, in women, is proposed to be hysterectomy.[387;388]

A systematic review of literature published between 1966 and 1997 on the association between hysterectomy and urinary incontinence identified 45 articles.[389] Of these, only 12 were eligible for inclusion in the review with other studies excluded for a number of reasons including a lack of non-hysterectomised comparison groups. While most of these 12 studies found an association between hysterectomy and increased risk of urinary incontinence, some studies found no significant association and other studies found a reduction in risk. In a meta-analysis of the results from all 12 studies, the majority of which were cross-sectional, significant heterogeneity between study results was found. To account for this heterogeneity results were stratified by age. These results suggested that hysterectomy was associated with an approximately 60% increased risk of incontinence in women ≥60 years but there was no significant association in younger women. The findings of this meta-analysis could potentially be limited by publication bias. Further, despite their inclusion in the review some of the 12 studies had limitations e.g. only two of the studies were considered to have adjusted appropriately for potential confounders such as age, parity and weight and, hysterectomy was sometimes grouped with other gynaecological surgery.

Since the publication of this review other studies[140;308;390-392] have also found an increased risk of urinary incontinence and severity of incontinence symptoms associated with hysterectomy. Unlike the findings from the systematic review these associations were not limited to the elderly and were shown to be significant even after adjustment for important confounders such as age, parity, BMI and educational level.

There are two main types of urinary incontinence: stress (urine leakage associated with abdominal pressure) and urge (urine leakage associated with a feeling of urgency). Most studies group both types together. However, this might not be appropriate as a Dutch cross-sectional study[140] found that hysterectomy was associated with urge but not stress incontinence, which is similar to the results from earlier analyses of the NSHD.[393]

While most studies seem to provide evidence that hysterectomy is associated with increased risk of urinary incontinence, some studies[394] have found no association and others have found an overall improvement in incontinence symptoms.[228;343;395;396] The studies which have found beneficial effects of hysterectomy are limited by the fact that they tend not to have non-hysterectomised comparison groups. Instead hysterectomised women are used as their own controls and pre-operative incontinence levels are compared with incontinence levels and symptoms post-hysterectomy. While such a study design is not ideal the fact that it produces opposing results to other studies suggests that it may be important to consider pre-operative incontinence levels which many of the studies finding a detrimental effect of hysterectomy have not done. This is especially important as hysterectomy could be a marker of pre-existing pelvic floor dysfunction and continence problems.

Less well studied than the association between hysterectomy and bladder function is the association between hysterectomy and bowel function. Recent reviews[310;397-399] have concluded that although some studies have found associations between hysterectomy and faecal incontinence, constipation and other outcomes associated with bowel function,[400-402] there is no clear and convincing evidence that there is an association. One of the major limitations of existing studies is that, as for studies of urinary incontinence, they lacked pre-operative measures of bowel function, used self-reported measures of function and did not adjust for confounders.

Hysterectomy could detrimentally affect bladder and bowel function through damage to pelvic nerves and support structures and alterations in the anatomical relationship between the pelvic organs caused by surgery.[308;343;389;391;402] Urinary tract damage is reported to occur during hysterectomy[403] and the effect of this damage may be evident immediately or take time to manifest. Another possible explanation of an association between hysterectomy and bowel function, proposed by Thakar,[397] is that women with abdominal pain even if caused by bowel problems are likely to primarily be referred to a gynaecologist who will often recommend hysterectomy. In this instance hysterectomy is a marker of pre-existing bowel problems which have initially been misdiagnosed as gynaecological problems. In studies which demonstrated an improvement in incontinence levels following hysterectomy it is possible that such an effect was found because bladder repair if identified as necessary was likely to be undertaken at the same time as hysterectomy.

8.2.3.8 Sexual function

Damage to pelvic nerves and support structures inflicted during hysterectomy could influence sexual function as well as bladder and bowel function.

There is conflicting evidence regarding the association between hysterectomy and sexual function, which comprises characteristics such as frequency of intercourse, libido, arousal, orgasm and sexual interest. A number of recent reviews[46;310;398;404-406] provide excellent summaries of the literature on this set of outcomes. Early studies of the association between hysterectomy and sexual function usually found a detrimental effect of hysterectomy whatever the measure of sexual function considered. Despite these studies having a number of major limitations, including a lack of comparison groups, retrospective designs and no measures of pre-hysterectomy sexual function, they led people to believe that hysterectomy was detrimental to subsequent sexual function.

The reviews show that more recent studies with comparison groups, some of which are prospective, have tended to find either no association between hysterectomy and sexual function or an improvement in sexual function post-surgery leading reviewers to conclude that there is no clear evidence of association and that hysterectomy is probably more likely to result in some improvements in sexual function with only a subgroup of women at risk of deterioration. In their review, Flory and colleagues,[406] examined a number of characteristics of sexual function finding no evidence of an association between hysterectomy and libido, arousal, orgasm or frequency of intercourse. They found that hysterectomy was associated with improved global sexual functioning and a reduction in dyspareunia (pain during sexual intercourse) and pelvic pain. This review discussed the fact that although a decrease in pain may be seen in women after hysterectomy the prevalence of this characteristic could still be higher than the prevalence amongst non-hysterectomised women which highlights the importance of including pre-hysterectomy measures. Farrell and Kieser[404] assessed the quality of all 18 studies included in their review and concluded that most were poor - there was a lack of validated outcome measures, little control for confounders (including relationship status and psychological health), lack of definition of outcomes, no objective measurement of outcomes and no consideration of reason for hysterectomy or route of operation. Despite highlighting the flaws of studies of sexual function, studies published since Farrell and Kieser's review still have not always included appropriate comparison groups[407;408] or considered pre-procedure levels of sexual function[409] which perhaps explains why conflicting results continue to be found.

There are plausible explanations of both detrimental and beneficial effects of hysterectomy on sexual function. In addition to the possible detrimental effect of hysterectomy caused by damage to the pelvic structure and nerves, hysterectomy could detrimentally influence sexual outcomes in a number of other ways. These include: a reduction in oestrogen and androgen exposure causing a reduction in sexual interest, vaginal atrophy and reduced lubrication, the latter of which would reduce arousal; disruption in blood circulation to the pelvis necessary for arousal and orgasm; a reduction in sensitive tissue; formation of scar tissue; and loss of the uterus which may have a role in the physiology of orgasm.[226;405;406] Beneficial effects of hysterectomy could result from relief of gynaecological symptoms and pelvic pain which may have limited sexual function prior to hysterectomy and the removal of fear of pregnancy and gynaecological disease.[226;398;406]

8.2.3.9 Psychological outcomes

Psychological health could explain any association between sexual function and hysterectomy as it influences components of sexual function such as libido and sexual frequency and is also potentially associated with hysterectomy.

There is a long history of debate about the potential association between hysterectomy and subsequent psychological outcomes, such as depression, anxiety and body image.[19;46;226;310;406;410] Ryan,[46] in her review of the psychological outcomes of hysterectomy, refers to Krafft-Ebing who in the 1890s suggested that hysterectomy was more likely to cause psychosis than any other surgical procedure. Ebing was not alone and the view that hysterectomy resulted in psychiatric morbidity was widely held for much of the twentieth century driven partially by the belief that the uterus played an important role in psychopathology in women.[44;406] However, as for studies of many other potential health consequences of hysterectomy, studies of psychological outcomes have conflicting findings. The majority of recent studies, which have applied more appropriate methodologies including adjustment for pre-hysterectomy psychological state, suggest that hysterectomy may not be associated with subsequent adverse psychological problems[46;310;319;406;410-412] except possibly in women who already have psychological problems pre-hysterectomy.[310;410] In their recent review of the literature, Flory and colleagues[406] considered depression, body image and global psychological function and found no convincing evidence for an association between hysterectomy and depression or psychiatric illness. However, while they found few studies which had considered body image, those that had suggested that hysterectomy may detrimentally affect this with the effect greatest for abdominal hysterectomies where chances of visible scarring are highest.

While the idea that the uterus (and therefore its removal) controls psychopathology has now been disregarded there are other reasons why an association between hysterectomy and psychological health may be seen other than solely because women with poor psychological health are more likely to undergo hysterectomy. Most of the proposed explanations for a detrimental effect of hysterectomy on psychological health are associated with the fact that hysterectomy may lead to a change in hormone levels which can affect mental health and that it can cause scarring and lead to a loss of feminine self image, strength and self esteem and feelings of distress at the loss of fertility.[8;406;413] Loss of anxiety about gynaecological problems and relief of symptoms may explain a beneficial effect.

The limitations of many existing studies are similar to those in studies of other outcomes and include: a lack of comparison groups; no adjustment for pre-hysterectomy measures of the outcome; no analyses by reason; and no adjustment for age at or time since hysterectomy.

Studies of associated outcomes such as quality of life, the literature on which has been reviewed by Rannestad[410] suggest that this measure, which may influence and be influenced by psychological health, improves in the years after hysterectomy. This is supported by evidence from randomised trials[414;415] which has demonstrated that for women with menstrual disorders improvements in quality of life up to 5 years after hysterectomy are found and that these improvements are sometimes greater than are gained from other less invasive treatments.[414]

8.2.3.10 Previous work using data from the NSHD

While no study using data from the NSHD has looked directly at the association between hysterectomy and subsequent health, a body of work aiming to assess the effect of the menopause on women's health outcomes in middle-age has compared women with hysterectomy to women in other menopausal states.[163;393;416-421] This work is summarised in appendix 7 and shows that hysterectomy may be associated with poorer CVD risk profile,[163] higher levels of somatic and psychological symptoms at age 47 years,[416] greater use of HRT[417] and increased risk of urge incontinence.[393] While hysterectomised women in the NSHD were also found to have a higher prevalence of sexual difficulties and trouble sleeping at age 47 years[416] and report greater declines in sexual function and increases in sexual difficulties between ages 47 and 54 years[421] compared to women who remained pre-menopausal the reported levels of these outcomes and changes in these were similar to those seen among women who became naturally post-menopausal. Hysterectomy did not appear to be associated with vasomotor symptoms at age 47 years,[416] changes in psychological or vasomotor symptom reporting or quality of life between ages 47 and 52 years[418;420] or in psychological symptom scores over this time period.[419]

As the effect of hysterectomy status has not been the main focus of these analyses there are understandable limits to the conclusions about the effect of hysterectomy which can be drawn from them. Many of the analyses were performed when women were in their late 40s and more hysterectomies have occurred since this time. There was no consideration of differences in effect by reason for hysterectomy, route of hysterectomy or oophorectomy status, there was no adjustment for time since hysterectomy and, often women whose hysterectomies were performed post-menopausally were classified as naturally menopausal rather than as hysterectomised and women who took HRT regardless of their menopausal/hysterectomy status were grouped together. Further, full adjustment for factors which could predict hysterectomy (rather than overall menopausal status) and subsequent outcomes independently were not performed and pre-hysterectomy health status was not always considered.

The work from the NSHD to date suggests that there are some differences in health outcomes by hysterectomy status which are worthy of further investigation.

8.2.4 Summary of limitations of previous studies

There are limitations common to existing studies of all health outcomes of hysterectomy. One of these is a lack of comparison groups. It is insufficient when studying most outcomes (with the exception of factors such as patient satisfaction) to include only hysterectomised women even if they are followed prospectively and their pre-hysterectomy measures are used for comparison with post-hysterectomy measures. Without comparison groups it is difficult to rule out the possibility that any effect of hysterectomy found could be explained by changes with age or some other factor which varied over time. Other limitations of existing studies include no consideration of common/shared risk factors, no adjustment for pre-hysterectomy health status and insufficient adjustment for potential confounders – factors such as HRT use, SEP, BMI and parity may confound the associations between hysterectomy and health outcomes and need to be considered.

Further limitations include a lack of consideration of potential differences in the effect of hysterectomy by different characteristics of the procedure including: route of hysterectomy; reason for hysterectomy; timing of hysterectomy; oophorectomy status; and menopausal status at the time of the procedure. This is despite the fact that there is evidence of and reasons to expect variation in most long-term health outcomes by all of these characteristics of hysterectomy.

8.2.4.1 Route of hysterectomy

A recent systematic review[422;423] and other research[424-430] suggests differences in outcome by route of hysterectomy which should not be ignored in analyses.

8.2.4.2 Reason for hysterectomy

Some gynaecological disorders and health outcomes could share underlying pathologies explaining the associations found between hysterectomy and these health outcomes, this cannot be identified unless consequences by reason for hysterectomy are examined. Further, hysterectomies for malignant reasons are likely to have different effects on health outcomes to those effects of hysterectomies for benign reasons. For example, the psychological implications of being diagnosed and treated for cancer would be expected to differ from those associated with being diagnosed with a benign condition. Further, reason for hysterectomy could be a marker of the extent of tissue removal which takes place during surgery, with hysterectomies performed for cancer more likely to involve greater pelvic disturbance through removal of a greater amount of tissue,[431] with differential effects in outcome such as sexual, bowel and bladder function thus expected by reason for hysterectomy.

8.2.4.3 Timing of hysterectomy

The effect of hysterectomy on many health outcomes is likely to be influenced by the age hysterectomy is performed. Younger women are likely to have better overall health status at the time of surgery and therefore be more likely to recover successfully and quickly from surgery. However, younger women are also likely to be at greater risk of feelings of regret associated with loss of fertility and be subject to hormonal changes further from the time when natural menopause would have occurred.

Variation in outcome by time since hysterectomy is expected as some effects of hysterectomy may be transient and so only seen in women immediately after their hysterectomies and while they are still in a recovery period. It is also possible that there could be a time lag between hysterectomy and the onset of some longer-term health consequences.

8.2.4.4 Oophorectomy status and menopausal status

Many of the health outcomes potentially associated with hysterectomy are influenced by hormonal exposure (e.g. musculoskeletal health, cancer, CVD) and so there is a need to consider factors other than hysterectomy associated with the procedure which influence hormone exposure more directly, i.e. oophorectomy and menopausal status.

8.2.5 Addressing the limitations of existing studies

The ideal way to address some of the limitations listed above would be to perform randomised controlled trials however there are often difficulties in performing these for a treatment such as hysterectomy.[432] More practical is to ensure that observational studies are undertaken which have improved methodology and take into consideration ways of avoiding as many of the potential limitations listed as possible.

The way in which the effect of hysterectomy on subsequent health outcomes is conceptualised needs addressing. There are a number of different ways in which hysterectomy and subsequent health outcomes could be associated. The three models in figure 8.1 are diagrammatical representations of some of the most widely proposed or tested of these. Model 1, the most simple, suggests that hysterectomy directly influences risk of long-term health outcomes and that this effect is independent of other factors including previous health status. Model 2, is an extension of model 1, and also proposes that there is a direct pathway between hysterectomy and health outcomes but in addition suggests that this pathway mediates the association between other risk factors and health outcomes. Model 3 proposes that there are a range of factors which predict risk of hysterectomy and also independently predict risk of other health outcomes. In this model, any associations found between hysterectomy and health outcomes would be explained by confounding by the factors which both hysterectomy and the health outcome are predicted by. This model also takes into consideration pre-hysterectomy health status and proposes that this influences risk of hysterectomy and also risk of health outcomes post-hysterectomy. It also allows for the fact that hysterectomy may have some influence on later health outcomes additional to that found due to its association with pre-hysterectomy health status. While the associations could be acting along all the arrows shown in model 3 with all pathways equally weighted, in reality it is more likely that not all pathways are operational and that of those that are they are unequally weighted. It is also likely that different models would be appropriate for different health outcomes.

Models 1 and 2 are the least realistic of the three but many studies of the consequences of hysterectomy have used similar frameworks. The limitation of this is clearly highlighted in the study of a number of outcomes including psychological health and sexual function in which there appeared to be an association between hysterectomy and subsequent poor health until prior health status was adjusted for. Model 3 represents a more realistic framework. A number of studies have now adjusted for prior health status finding that it is important to consider this. This is especially so given that in cross-sectional studies women who have undergone hysterectomy could be found to have poorer health than women with intact uteri even if hysterectomy has actually resulted in improvements in health status. Not considering this could lead to the wrong conclusions about the effect of hysterectomy being made.

It is only recently that researchers have begun to consider the possibility that the relationship between hysterectomy and health outcomes could result from common pathways influencing risk of both hysterectomy and health outcomes independently. While a number of authors,[129;130;144;175;331;332;336] mainly of studies of CVD risk, have proposed this model it is usually in their discussions and is not something they have been able to test. Given the plausibility of this there is a need to test it for most long-term outcomes and to do this it is necessary to know what the life course predictors of hysterectomy and the outcome under study are.

8.3 The health consequences examined in this thesis

It is not possible with data from only one cohort with a limited set of appropriate measurements to examine all plausible health consequences of hysterectomy satisfactorily. For this reason only a small number of consequences, which can be suitably studied using the data from the NSHD, have been examined.

Potential long-term rather than short-term health consequences of hysterectomy have been selected for study. This is for a number of reasons. Firstly, there is much less dispute about the association between hysterectomy and short-term consequences as these can usually be directly attributed to the fact that women have undergone major surgery. Secondly, using the NSHD, which has collected data on all cohort members at specific ages rather than on individual members at the time when they have undergone surgery it would be difficult to study the short-term consequences of hysterectomy as the relevant data is not available. In addition many of the short-term effects of hysterectomy have less importance when considering the role of hysterectomy in influencing health across the remainder of life as they are more likely to only be transient.

Of the long-term consequences, the women in the NSHD are not old enough to have developed chronic diseases or died in sufficient numbers for many diseases or mortality to be investigated with sufficient power yet. Further, the cohort is not large enough for sufficient cases of some rare outcomes, including many cancers, to ever be studied with sufficient power. Instead this thesis focuses on: body weight; musculoskeletal health; and psychological health and perceptions of the effect of hysterectomy on quality of life and wellbeing. These are all important outcomes in their own right and could precipitate chronic conditions in later life.

8.4 Methods

To avoid repetition, the methods used to examine the consequences of hysterectomy common to all three chapters are described below with more specific details provided where necessary in the appropriate chapters.

8.4.1 Study population

As for the study of the predictors of hysterectomy, the study population used to assess the consequences of hysterectomy consisted of all women in the NSHD with valid information on hysterectomy status and a valid date for hysterectomy if they had undergone this procedure (N=1,790). Women were excluded from analyses if their hysterectomy or oophorectomy was performed at or after the age of outcome measurement given these analyses aimed to test the effect of hysterectomy on *subsequent* health.

8.4.2 Main outcome variables

These and their ascertainment are described in the relevant chapters.

8.4.3 Main explanatory variable

Hysterectomy status, method of ascertainment described in chapter 2.

8.4.4 Categorisation of explanatory variable

Hysterectomy status was categorised into three groups for each of the main sets of analyses: hysterectomy with or without oophorectomy; unilateral or bilateral oophorectomy; no hysterectomy or oophorectomy. The women who had an oophorectomy only were categorised separately as it was thought that the loss of ovarian function associated with the procedure may influence each outcome and make this group of women different to the no-hysterectomy group but, as the surgery was less major than a hysterectomy and performed for a different set of reasons, also different to the hysterectomy group.

To maximise power in the main analyses all hysterectomies were grouped together however, as described in section 8.2, it is possible that there is variation in the effect of hysterectomy by characteristics of hysterectomy and failing to take this into account would be a limitation. For this reason, in each of the following three chapters variation in the effect of hysterectomy by characteristics of hysterectomy which could plausibly affect the outcomes have been examined. These characteristics were: oophorectomy status; reason for hysterectomy; route of hysterectomy; age at hysterectomy; and menopausal status at time of hysterectomy. The categorisations of these characteristics used were:
- *oophorectomy status*: no hysterectomy or oophorectomy; hysterectomy only; hysterectomy with unilateral or bilateral oophorectomy; oophorectomy only
- *reason for hysterectomy*: no hysterectomy or oophorectomy; hysterectomy for fibroids; hysterectomy for menstrual disorders; hysterectomy for prolapse; hysterectomy for cancer; hysterectomy for other known reasons; hysterectomy for unknown reasons
- *route of hysterectomy*: no hysterectomy or oophorectomy; abdominal hysterectomy; vaginal hysterectomy; unknown route
- *age at hysterectomy*: no hysterectomy or oophorectomy; hysterectomy at age: < 40 years; 40 – 44 years; 45 – 49 years or; ≥50 years

- *menopausal status at time of hysterectomy*: no hysterectomy or oophorectomy; pre-menopausal hysterectomy; post-menopausal hysterectomy

The methods used to ascertain each of these characteristics were described in chapter 2.

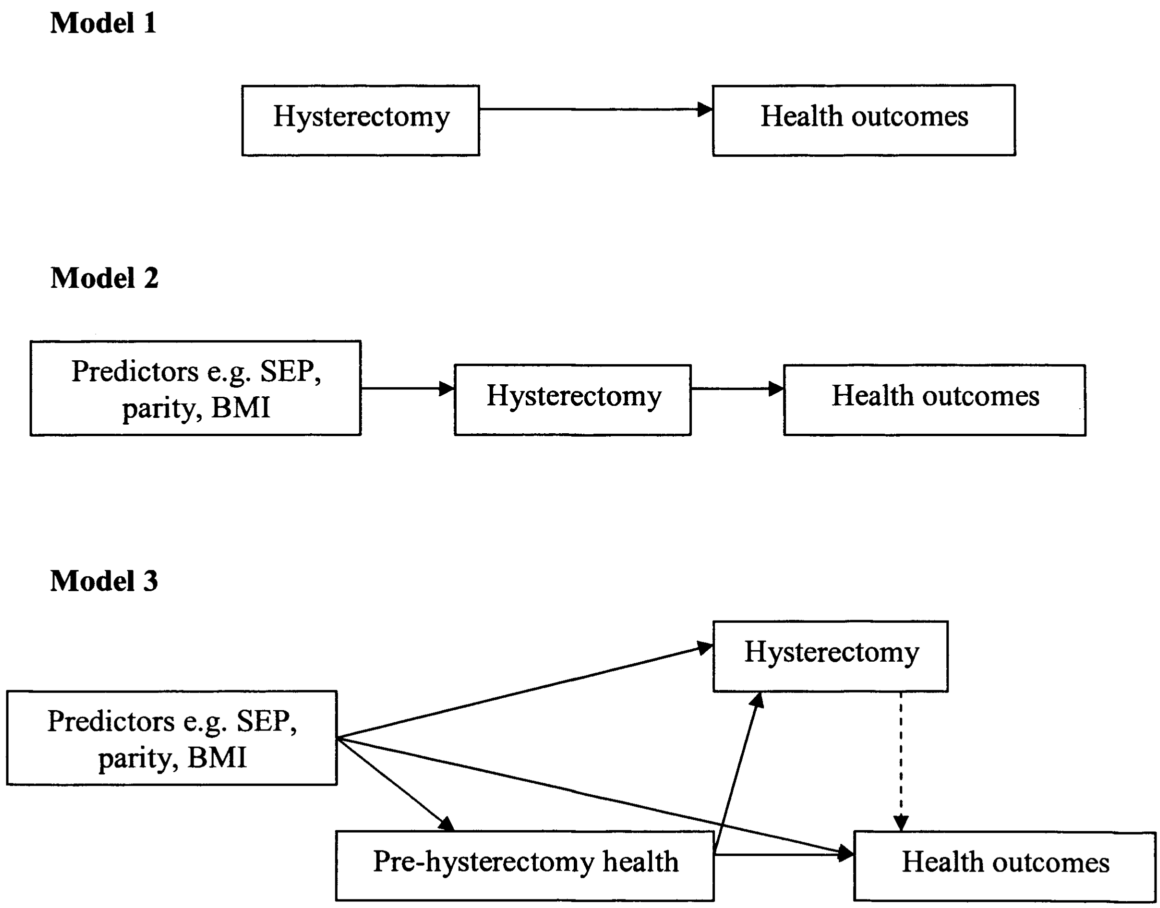
8.4.5 Covariates

Variables from across life which could confound the main associations of interest, i.e. which have been found to be associated with the outcome and also with risk of hysterectomy, were identified and adjusted for in analyses. If there was reason to expect that any particular covariate could modify the effect of the association rather than confound it, tests for interaction were performed. Details of the covariates identified are specific to each outcome and so are presented in the relevant chapters which follow. It should be noted that all covariates were selected a priori based on findings from chapters 4 to 7 and from existing evidence in the literature.

8.4.6 Allowing for the stratified sampling procedure

Results from weighted analyses were compared to results from the equivalent unweighted analyses and as weighting the analyses did not alter the findings the results from unweighted analyses are presented.

Figure 8.1: Models of the association between hysterectomy and subsequent health outcomes



Chapter 9: Hysterectomy and subsequent body weight

Main objective: To investigate whether hysterectomy is associated with subsequent body weight.

9.1 Introduction

This chapter investigates the association between hysterectomy and subsequent body weight, an important outcome given the significance of body weight to women and, body weight's relationship with a range of chronic disease outcomes.

The review of previous studies of the association between body weight and hysterectomy in chapter 5, which to avoid repetition will only be summarised here, provided justification for further, detailed examination of this association. Most importantly the need to establish in which directions the association is acting was recognised especially as most existing studies are cross-sectional, a major limitation given there are plausible mechanisms by which weight could predict subsequent hysterectomy risk and by which hysterectomy could predict subsequent weight. The analyses in chapters 5 and 7 provide evidence to suggest that BMI from early adulthood onwards predicts subsequent hysterectomy rates in the NSHD. This chapter completes the story by examining the influence of hysterectomy status on subsequent BMI, taking into account the findings from these earlier chapters.

9.2 Summary of literature

As reported in chapter 5, not all existing studies of the association between hysterectomy and subsequent body weight are consistent. These studies are limited, if not by the fact that they are cross-sectional, by a reliance on self-reported measures of weight and height, short follow-up, small sample size, different methods of data collection for hysterectomised and comparison groups and/or a lack of control for confounders, all limitations which can be overcome using data from the NSHD. Further, no studies have assessed whether there are differences in the association between hysterectomy and subsequent body weight by characteristics of hysterectomy such as route of and reason for operation even though such characteristics could, as shown in chapter 8, influence outcome.

The lack of control for confounders is a major limitation of the majority of existing studies. To ensure analyses in this chapter were not limited in the same way factors from across life associated with BMI in middle-age and also associated with hysterectomy risk have been included in analyses in this chapter. The evidence used to inform selection of these covariates is summarised below.

In light of the findings from chapters 5 and 7 it was important to adjust for a measure of pre-hysterectomy weight. The association between BMI in adulthood and subsequent hysterectomy rates suggests that an association between hysterectomy and subsequent weight could be found due to these differences in weight pre-procedure rather than because differences in weight have developed as a direct consequence of hysterectomy especially as weight in earlier life predicts weight in later life.[200]

Indicators of lifetime SEP were found to be associated with hysterectomy in the NSHD, see chapter 4. There is evidence from the NSHD and other studies that lifetime SEP is also associated with adult body weight.[201;274;433;434] Age at menarche and parity were also found to be associated with hysterectomy in the NSHD (see chapter 6) and these are both characteristics which are associated with body weight in middle-age.[201;208;256;282;434] It has been found in studies including the NSHD that women who undergo hysterectomy are more likely to use HRT than other women.[417] Although there was no evidence from a systematic review of randomised controlled trials that HRT use influences weight,[435] women in the NSHD on HRT had lower mean BMI than naturally post-menopausal women[163] which has also been found in another study,[436] possibly because of a 'healthy user' effect.[437] Finally, although the association between exercise levels and hysterectomy has not been tested in the NSHD, other studies have found an association between hysterectomy and exercise levels,[142;154] with women who had hysterectomy leading more sedentary lives than other women, a characteristic also strongly associated with BMI at all ages.[201] On the basis of this evidence, pre-hysterectomy weight, lifetime SEP, reproductive characteristics, HRT use and exercise levels all needed to be considered in the analyses of the association between hysterectomy and subsequent weight.

9.3 Specific objectives of the chapter

The specific objectives to be addressed in this chapter are:

i. to examine whether hysterectomy is associated with subsequent BMI
ii. to examine whether the association between hysterectomy and subsequent BMI differs by oophorectomy status, reason for and route of operation, age at hysterectomy and menopausal status at time of hysterectomy
iii. to examine whether the association between hysterectomy and subsequent BMI is independent of BMI in earlier life (pre-hysterectomy) and factors which predict BMI in middle-age and hysterectomy risk

9.4 Methods

9.4.1 Main outcome variables

BMI at age 53 years, method of ascertainment described in chapter 5. BMI at this age was selected as it was the most recent BMI measurement and is at an age by which time most hysterectomies had occurred. BMI rather than some other measure of weight or body composition was used for the reasons provided in chapter 5.

9.4.2 Main explanatory variable

Hysterectomy status

9.4.3 Covariates

BMI at age 36 years, age at menarche, parity at age 53 years, lifetime SEP (father's occupational class in childhood, maternal education level, own occupational class in adulthood and educational level attained), exercise levels at ages 36 and 53 years, history of HRT use at age 53 years

9.4.4 Exclusions

Women whose hysterectomy or oophorectomy was performed at or after age 53 years (given these analyses aimed to test the association between hysterectomy and *subsequent* BMI).

9.4.5 Ascertainment of covariates

Details of the ascertainment of BMI at age 36 years were provided in chapter 5, of age at menarche and parity in chapter 6 and of the four measures of SEP in chapter 4. BMI at age 36 years and age at menarche were included in analyses as continuous variables, parity at age 53 years was grouped into 5 categories (no children; 1; 2; 3; ≥4 children), father's and own occupational class into 4 categories (I or II; IIINM; IIIM; IV or V), maternal education into 4 categories (secondary and further or higher education; secondary only or, primary and further or higher education; primary and further education (no qualifications attained); primary education only) and educational level attained by age 26 years into 5 categories (Degree or higher; 'A' levels or equivalent; 'O' levels or equivalent; CSE, clerical course or equivalent; None).

Exercise levels at ages 36 and 53 years were ascertained from questions asked during home visits. At age 36 years women were asked about their level of participation in 27 sports and recreational activities, this information was aggregated to create an overall exercise level.[438] At age 53 years women were asked on how many occasions in the last four weeks they had taken part in any sports or vigorous leisure activities or done any exercises in their spare time. At both ages exercise level was grouped into three categories: none; 1-4 times a month; > 4 times a month.

History of HRT use at age 53 years was ascertained from information collected during the 1999 home visit and provided in response to questions in the 'Women's Health in the Middle Years' postal questionnaires. This variable was grouped into three categories: never used; current user; ex-user.

9.4.6 Analyses

9.4.6.1 Analyses to address objective (i) – unadjusted associations

A comparison of mean BMI at age 53 years by prior hysterectomy status was performed using one-way analysis of variance and a linear regression model. Checks to ensure that standard deviations were similar and BMI was approximately normally distributed in each category of hysterectomy status by plotting histograms confirmed that it was appropriate to use these methods of analysis.

9.4.6.2 Analyses to address objective (ii) – characteristics of hysterectomy

Comparisons of mean BMI at age 53 years by each characteristic of hysterectomy (categorisations described in section 8.4.4) were performed using one-way analysis of variance and linear regression models.

Using likelihood ratio tests, regression models of the association between each characteristic of hysterectomy and subsequent BMI were compared to a linear regression model in which all hysterectomies were grouped together. Women who had undergone an oophorectomy only were excluded from all analyses except those assessing the difference in association by oophorectomy status.

9.4.6.3 Analyses to address objective (iii) – adjusted associations

Using multiple regression models the association between hysterectomy status (no hysterectomy or oophorectomy; hysterectomy with or without oophorectomy) and subsequent BMI at age 53 years was adjusted in separate models for: BMI at age 36 years; age at menarche; parity at age 53 years; lifetime SEP (father's occupational class in childhood, maternal education, educational level attained and own occupational class in adulthood); exercise levels at age 36 and 53 years; and history of HRT use. Where appropriate, likelihood ratio tests were performed to examine whether variables were most appropriate to be entered as continuous or categorical terms. Further likelihood ratio tests were performed to test for interaction between HRT use, BMI at 36 years and hysterectomy status as it was thought these variables may modify the association rather than confound it. As BMI at age 36 years was included as a measure of pre-hysterectomy BMI, the models including BMI at age 36 years excluded not only women whose hysterectomy or oophorectomy occurred at or after age 53 years but also those performed at or before age 36 years.

In a final set of models including only those women with complete data on hysterectomy status, BMI at ages 36 and 53 years and all other important covariates and, whose surgery was performed between ages 36 and 53 years, the association between hysterectomy status and BMI at age 53 years adjusted for each set of covariates were tested in individual models. Different sets of covariates were then adjusted for in the same models, before all variables were adjusted for in a final model. All of the variables which likelihood ratio tests suggested improved the fit of the model were included in these analyses.

Women who had had an oophorectomy only were excluded from all multivariable models presented as the regression coefficients estimated for the oophorectomy only group were unstable i.e. had very wide confidence intervals and varied greatly dependent on the sample included, possibly because the number of women in this group was small.

9.5 Results

9.5.1 Results from analyses to address objective (i) - unadjusted associations

Women who had previously had a hysterectomy had a mean BMI 0.85kg/m^2 higher at age 53 years than women who had not undergone a hysterectomy or oophorectomy, this difference was statistically significant, table 9.1.

9.5.2 Results from analyses to address objective (ii) - characteristics of hysterectomy

There was no evidence from likelihood ratio tests that categorising hysterectomy by any one of the characteristics was significantly different to grouping all hysterectomies together, table 9.2. However, some categories of women i.e. women who had hysterectomies for fibroids, women who had vaginal hysterectomies and women who had pre-menopausal hysterectomies did have significantly higher BMI than women who had not had a hysterectomy or oophorectomy as indicated by the fact that the 95% confidence intervals for the mean differences in BMI between these groups did not include 0.

9.5.3 Results from analyses to address objective (iii) - adjusted associations

The association between hysterectomy status and BMI at age 53 years attenuated after adjustment for BMI at age 36 years, with the difference in mean BMI at age 53 years between the no hysterectomy and hysterectomy groups reducing from 0.81 kg/m^2 to 0.28 kg/m^2 and becoming non-significant, table 9.3. Individual adjustment for each of the other covariates except HRT use also attenuated the difference in mean BMI at age 53 years between the no hysterectomy and hysterectomy groups. Conversely adjustment for HRT use increased the difference in mean BMI at age 53 years by hysterectomy status and the association became more significant. There was no evidence of interaction between hysterectomy status and HRT use or BMI at age 36 years.

The above findings were confirmed in analyses restricted to women with complete data on all variables except lifetime SEP, measures of which were not included in the final models because they did not have a strong confounding effect and likelihood ratio tests suggested there was no benefit in including them in fully adjusted models. However, with the restriction in sample even the unadjusted association was non-significant, table 9.4. Adjusting for BMI at age 36 years caused a greater reduction in the difference in mean BMI at age 53 years between the no hysterectomy and hysterectomy groups than individual adjustment for age at menarche and parity or exercise at ages 36 and 53 years. Adjustment for all three sets of variables reduced the difference in mean BMI at age 53 years by a slightly greater amount than any one factor by itself. Including HRT use increased this estimate slightly because its effect was acting in the opposite direction - hysterectomy was associated with increased HRT use and HRT use was associated with lower BMI, possibly because of a 'healthy user' effect. In a fully adjusted model the difference in mean BMI at age 53 years between women who had had a hysterectomy and those who had not was 0.26 kg/m^2, this was not statistically significant.

9.6 Discussion

9.6.1 Main findings

In unadjusted analyses women who had had a hysterectomy with or without oophorectomy had significantly higher BMI at age 53 years than women who had not undergone a hysterectomy or oophorectomy, this difference was less than 1 kg/m^2. The association did not differ significantly by any of the main characteristics of hysterectomy. After adjustment for pre-hysterectomy BMI, age at menarche, parity, exercise levels in adulthood and HRT use the association between hysterectomy and subsequent BMI attenuated and was no longer significant.

9.6.2 Comparison with other studies

Very few studies had designs which were appropriate to satisfactorily test whether hysterectomy does predict subsequent body weight with different studies producing results which were not fully consistent with each other. This study is an improvement on what has been done previously. While the unadjusted association between hysterectomy and subsequent BMI was significant in the NSHD, supporting the findings from those previous studies which did find evidence of an association, this was explained by pre-hysterectomy BMI and other confounders, which is probably why some other studies did not find associations. In studies where women were asked for their subjective views on the effects of their hysterectomy many cited weight gain as a detrimental consequence of hysterectomy.[228;229] The results from this study suggest that women may have incorrectly attributed their weight gain to hysterectomy.

9.6.3 Explanation of findings

Women who at 53 years had previously had a hysterectomy had significantly higher BMI at this age than women who had not had a hysterectomy or oophorectomy. This finding does not however appear to be due to a direct effect of hysterectomy on BMI. Instead the results suggest that women who had a hysterectomy were already on a trajectory of slightly increased weight compared to other women prior to surgery (which supports the results found in chapter 5 which suggested that increasing weight across adult life was a risk factor for subsequent hysterectomy). Hysterectomised women were also more likely to have greater levels of other risk factors for higher BMI in middle-age such as high parity, early age at menarche and lower exercise levels across adult life overall than other women.

That there were no differences in effect by any of the characteristics of hysterectomy supports the notion that there is no direct effect of hysterectomy on body weight as it suggests that none of the plausible mechanisms of association between hysterectomy and subsequent BMI were operating. For example, if hysterectomy was affecting subsequent BMI through its damaging influence to fat and muscle tissue in the abdomen when surgical incisions were made, or was influencing BMI by causing a period of ill health and low activity while women recuperate and recover from the procedure it would be expected that women who had undergone abdominal hysterectomy would have greater weight than women who had undergone a vaginal hysterectomy, given vaginal hysterectomies do not involve making incisions in the abdomen and have a shorter recovery time. However, there was no significant difference in the effect of hysterectomy by route of procedure. Likewise if hysterectomy affected subsequent BMI through its effect on feelings of loss of fertility and femininity which lead to reductions in activity levels and increases in calorie consumption it would be expected that women who had earlier hysterectomies, and therefore lost more of their reproductive years, would have been more greatly affected in this way and would have greater weight but there was no evidence of such an effect.

Further evidence that hysterectomy is unlikely to have detrimental effects on activity levels, through its impact on psychological health, because of the time required to recuperate and fully recover from the procedure or along some other pathway, comes from comments women made in response to the question in the 2005 questionnaire which asked them how their hysterectomy had affected their subsequent wellbeing and quality of life. Comments such as:

'Made me feel more energetic'

'Meant I was able to get on with my life and participate in sports'

'Having more energy instead of feeling tired all day'

'Greater energy, less discomfort'

'Increased ability to participate in outdoor/camping/hiking activities'

imply that while women's activity levels were affected and limited by the symptoms of gynaecological conditions, hysterectomy removed these effects and led to increases in activity rather than the reverse.

9.6.4 Limitations

In the discussion in chapter 5, it was shown that despite some limitations BMI was an appropriate measure of overall adiposity for use in analyses. However, BMI does not indicate differences in body fat distribution. In terms of assessing the consequences of hysterectomy across the remainder of life, assessing the effect of hysterectomy on measures of body fat distribution may have been more relevant especially as many recent studies have shown that measures of central adiposity (i.e. waist circumference and waist:hip ratio) are better predictors of subsequent cardiovascular and other chronic disease risk than

BMI.[246;247;439;440] BMI was used as the main outcome in this chapter to maintain consistency between the analyses in this chapter and those in chapter 5 and, because measures of central adiposity were only available at ages 43 and 53 years in the NSHD. However, in analyses which assessed the effect of prior hysterectomy on waist circumference and waist:hip ratio at 53 years (results not shown) there were no significant differences in the mean levels of these outcomes by hysterectomy status suggesting that hysterectomy was not associated with subsequent central adiposity.

To ensure that the association being tested was between hysterectomy and subsequent BMI all hysterectomies performed at or after age 53 years had to be excluded. It was thus not possible to test whether hysterectomies performed at later ages had a different effect to those performed before age 53 years. However, as there was a downward trend in rates of hysterectomy being performed by age 53 years this is not a major limitation. In adjusted analyses women whose hysterectomies occurred prior to age 36 years were also excluded. This is unlikely to have altered the findings greatly as there was no evidence of significant differences in association by age of hysterectomy.

Although there may be no real differences in effect of hysterectomy on weight by characteristic of hysterectomy it is also possible that there were undetected effects because of lack of power in analyses, especially as in some categories of characteristic used there were very few women (e.g. only 8 women underwent post-menopausal hysterectomies).

While factors which it was thought a priori could confound the main association of interest were controlled for in analyses it is possible that there was residual confounding in the fully adjusted models because not all important confounders had been identified and because some characteristics adjusted for had not been adequately defined. For example, HRT use at age 53 years was included as a simple 3 category variable despite the fact that there are different types of HRT preparation with differing health effects and wide variations in duration of use. However, as potential confounders from across life and measured at more than one time were included in analyses this will have minimised residual confounding.

HRT use and exercise at age 53 years were included in analyses as confounders, however, it may have been inappropriate to adjust for these factors as they could have been mediating the association. This is unlikely to be a major limitation as even when these two variables were not included in adjusted models and only variables which came in time before both hysterectomy and BMI at age 53 years (and so by definition could not mediate the association) were included in models the association between hysterectomy and BMI attenuated to the point of non-significance.

The analyses which could be performed were limited by the data available and the sample size. It would have been interesting to examine the association between hysterectomy and *subsequent* changes in weight but because weight was only measured at 10 year intervals in later adulthood and the majority of hysterectomies occurred between the last two major data collection points (i.e. ages 43 and 53 years) any analyses of the association between hysterectomy and subsequent BMI change would have been restricted to hysterectomies occurring before age 43 years and so would have had limited power and generalisability. It will be possible to examine such effects after the next planned data collection and also to investigate whether larger differences in body weight and composition between the different hysterectomy status groups develop at later ages.

9.6.5 Strengths

As in the study of the association between BMI and subsequent hysterectomy rates, the major strength of these analyses is the temporal nature of the data and the repeated collection of height and weight at time points across life. This has made it possible to separate out the effect of hysterectomy on weight from the effect of weight on hysterectomy. Further strengths compared to previous studies include the fact that the measures of BMI used have been calculated using heights and weights collected prospectively by trained health professionals rather than recalled and/or self-reported. As there is information available on a range of characteristics of hysterectomy it has been possible to examine differences in effect by these factors.

The wealth of information prospectively collected about the NSHD at time points across life has made it possible to adjust for a range of factors from across life which could confound the main association of interest.

The NSHD were selected to be nationally representative and despite losses to follow-up have remained largely so whereby the results from these analyses may be more generalisable to a national UK population than other studies, especially as no previous study has examined this association in a UK population.

9.6.6 Conclusions and implications

This study has demonstrated that women who had undergone hysterectomy had significantly higher BMI in middle-age than women who had not undergone hysterectomy or oophorectomy, however, this difference was less than 1 kg/m^2 and so is unlikely to be clinically important. Further, this difference was not due to a direct effect of hysterectomy on subsequent weight or body composition. Instead, hysterectomised women had higher BMI than other women because they possessed more risk factors for being of high BMI in middle-age than other women.

Women can thus be reassured that they are unlikely to experience weight gain as a direct result of hysterectomy. As these women do represent a group at increased risk of slightly higher BMI in middle-age than other women they are however, a defined group on whom advice about weight could be targeted especially as higher BMI is associated with increased risk of a range of chronic diseases in later life.

Table 9.1: Mean BMI (kg/m^2) and unadjusted differences in mean BMI at age 53 years by hysterectomy status in the NSHD

Hysterectomy status	N	Mean BMI (kg/m^2) at age 53 years (SD)	Regression coefficient (95% CI)
No hysterectomy or oophorectomy	1128	27.24 (5.48)	0.00
Hysterectomy*	314	28.08 (5.20)	0.85 (0.16, 1.53)
Oophorectomy only†	20	28.04 (7.35)	0.81 (-1.61, 3.22)
Total	1462	27.42 (5.46)	
p-value (F test)			0.046

* with or without oophorectomy
† bilateral or unilateral

Table 9.2: Mean BMI (kg/m^2) and unadjusted differences in mean BMI at age 53 years by characteristics of hysterectomy in the NSHD (N=1,462 for analyses including oophorectomy only group, N=1,442 for all other analyses)

Characteristic of hysterectomy	N	Mean BMI (kg/m^2) at age 53 years (SD)	Regression coefficient (95% CI)
No hysterectomy or oophorectomy	1128	27.24 (5.48)	0.00
Hysterectomy with oophorectomy†	166	28.01 (5.45)	0.77 (-0.12, 1.66)
Hysterectomy no oophorectomy	148	28.17 (4.93)	0.93 (-0.01, 1.86)
Oophorectomy only†	20	28.04 (7.35)	0.81 (-1.61, 3.22)
p-value			*0.80*
No hysterectomy or oophorectomy	1128	27.24 (5.48)	0.00
Hysterectomy for: Fibroids	105	28.52 (5.58)	1.28 (0.20, 2.37)
Menstrual disorders	98	27.79 (5.01)	0.55 (-0.57, 1.67)
Prolapse	28	26.60 (4.53)	-0.64 (-2.68, 1.40)
Cancer	19	27.89 (4.65)	0.65 (-1.81, 3.11)
Other reasons	48	28.44 (5.57)	1.20 (-0.37, 2.77)
Unknown reasons	16	28.81 (4.49)	1.58 (-1.10, 4.26)
p-value			*0.61*
No hysterectomy or oophorectomy	1128	27.24 (5.48)	0.00
Route of hysterectomy: Abdominal	239	27.87 (5.10)	0.63 (-0.13, 1.39)
Vaginal	56	28.78 (5.26)	1.54 (0.09, 3.00)
Unknown	19	28.75 (6.29)	1.51 (-0.95, 3.96)
p-value			*0.45*
No hysterectomy or oophorectomy	1128	27.24 (5.48)	0.00
Age at hysterectomy (years): < 40	87	28.40 (5.47)	1.16 (-0.03, 2.34)
40 - 44	81	28.16 (4.83)	0.92 (-0.31, 2.14)
45 - 49	100	27.82 (4.94)	0.58 (-0.53, 1.69)
≥50	46	27.95 (5.97)	0.71 (-0.89, 2.31)
p-value			*0.90*
No hysterectomy or oophorectomy	1128	27.24 (5.48)	0.00
Pre-menopausal hysterectomy	306	28.16 (5.19)	0.92 (0.24, 1.61)
Post-menopausal hysterectomy	8	25.19 (5.34)	-2.05 (-5.82, 1.73)
p-value			*0.13*

† bilateral or unilateral oophorectomy

Note: p-values from likelihood ratio tests comparing model with categorisation of hysterectomy shown with a model in which all hysterectomies were grouped together (women with oophorectomy only excluded from all models except those examining oophorectomy status)

Table 9.3: Differences in mean BMI (kg/m^2) at age 53 years by hysterectomy status adjusted for individual sets of variables in the NSHD

Adjusted for:	Regression coefficient (95% CI)		p-value
	No hysterectomy or oophorectomy	Hysterectomy with or without oophorectomy	
BMI at age 36 years (N=1268 – hysterectomies performed at age ≤36 years excluded)			
Unadjusted	0.00	0.81 (0.08, 1.55)	0.03
Adjusted	0.00	0.28 (-0.18, 0.75)	0.23
Age at menarche (N=1141)			
Unadjusted	0.00	0.69 (-0.09, 1.47)	0.08
Adjusted	0.00	0.53 (-0.24, 1.30)	0.18
Parity at age 53 years (N= 1441)			
Unadjusted	0.00	0.84 (0.16, 1.52)	0.02
Adjusted	0.00	0.76 (0.08, 1.44)	0.03
Lifetime SEP (N=1167)			
Unadjusted	0.00	1.05 (0.29, 1.81)	0.007
Adjusted	0.00	0.85 (0.11, 1.60)	0.02
Exercise at ages 36 and 53 years (N=1317)			
Unadjusted	0.00	0.89 (0.19, 1.60)	0.01
Adjusted	0.00	0.83 (0.14, 1.51)	0.02
Hormone replacement therapy use (N=1442)			
Unadjusted	0.00	0.85 (0.17, 1.53)	0.01
Adjusted	0.00	1.27 (0.56, 1.98)	0.0005

Table 9.4: Fully adjusted differences in mean BMI (kg/m^2) at age 53 years by hysterectomy status in the NSHD (N=1,024, No. of hysterectomies=208)

Variable/s adjusted for:	Regression coefficient (95% CI)		p-value
	No hysterectomy or oophorectomy	Hysterectomy with or without oophorectomy	
Unadjusted	0.00	0.57 (-0.26, 1.41)	0.18
BMI at age 36 years	0.00	0.26 (-0.24, 0.77)	0.31
Age at menarche; Parity	0.00	0.30 (-0.53, 1.12)	0.48
Exercise at ages 36 and 53 years	0.00	0.49 (-0.33, 1.30)	0.24
BMI at 36 years; Age at menarche; Parity	0.00	0.20 (-0.31, 0.71)	0.44
BMI at 36 years; Age at menarche; Parity; Exercise at 36 and 53 years	0.00	0.19 (-0.32, 0.70)	0.46
HRT use	0.00	0.94 (0.08, 1.81)	0.03
Fully adjusted*	0.00	0.26 (-0.26, 0.79)	0.33

* Adjusted for BMI at age 36 years, age at menarche, parity, exercise at ages 36 and 53 years, and HRT use

Chapter 10: Hysterectomy and musculoskeletal health

Main objective: To investigate whether hysterectomy is associated with subsequent musculoskeletal health.

10.1 Introduction

Musculoskeletal health is a global term used to describe the condition of the musculoskeletal system, which comprises bone, muscle and cartilage. The development and maintenance of good musculoskeletal health is influenced by factors acting across life and is essential to ensure successful ageing.[441] Poor levels of, and declines in, musculoskeletal health lead to frailty, disability and loss of independence in old-age,[442-444] all outcomes which are becoming increasingly prevalent and causing growing concern across much of the developed world as populations age. Absolute levels of, and declines in musculoskeletal health, even in non-disabled populations, are also significant predictors of subsequent mortality.[443;445;446] Understanding the determinants of musculoskeletal health is thus important. One potential predictive factor in women, who tend to have poorer musculoskeletal health than men,[447] is hysterectomy.

10.2 Summary of literature

As reported in chapter 8, section 8.2.3.6, existing studies have examined the effect of hysterectomy on bone density with results which are inconsistent across studies. In a systematic search of the literature no studies examining the effect of hysterectomy on other components of musculoskeletal health were identified despite there being plausible reasons to expect associations.

In summary, hysterectomy could influence musculoskeletal health through its effect on exposure to endogenous oestrogen and other hormones, HRT use, activity levels, or BMI. Alternatively, as highlighted in chapter 8 associations could exist because gynaecological conditions, hysterectomy and musculoskeletal function share common risk factors. The lack of any evidence despite the plausibility of association provides the justification for further research.

Factors from across life which could act as confounders needed to be identified and taken into consideration. These factors, similar to those considered in the previous chapter, include lifetime SEP which analyses in chapter 4 suggest predict hysterectomy rates, and which a series of papers using data from the NSHD suggest also predict musculoskeletal function.[447-450] Women of lower SEP experienced higher rates of hysterectomy in earlier adulthood and poorer musculoskeletal health than women of higher SEP. Age at menarche and age at first birth were both inversely associated with hysterectomy rates in the NSHD (see chapter 6). Analyses of data from the NSHD (not yet published) suggest that these two reproductive characteristics were also associated with musculoskeletal health outcomes at age 53 years. The association between age at first birth and musculoskeletal health was particularly strong, women who had a young age at first birth experienced poorer musculoskeletal health at age 53 year than women with later age at first birth. Although not yet investigated, it is possible that having children at a young age is in some way damaging to the musculoskeletal system or that the association is explained by SEP given age at first birth is socioeconomically graded.

In chapter 5, BMI in adulthood was found to be associated with subsequent hysterectomy rates. Measures of height and weight from across life have also been found to significantly predict musculoskeletal health in the NSHD.[447;448;450;451] Women of higher weight performed more poorly in tests of postural balance and chair rising but performed better in tests of grip strength, measures of musculoskeletal function, than women of lower weight. As mentioned in the previous chapter, although not examined in the NSHD, there is evidence from other studies that exercise may be associated with hysterectomy risk.[142;154] Levels of activity have also been found to predict musculoskeletal outcomes in the NSHD and other studies with more active women found to have better musculoskeletal health than less active women.[447;452;453] This could be because physical activity strengthens the musculoskeletal system and prevents declines in musculoskeletal function or because the activity levels of women who have poor musculoskeletal health are limited by their condition.

Also mentioned in the previous chapter was the fact that hysterectomised women in the NSHD were more likely to use HRT than other women.[417] Although results from different studies are not consistent, there is some evidence that HRT use may be associated with favourable musculoskeletal health[363-366;454] possibly because it maintains levels of oestrogen exposure protecting women from reductions in oestrogen levels which may lead to deterioration of the musculoskeletal system.

On the basis of this evidence lifetime SEP, reproductive characteristics, BMI, exercise levels and HRT use need to be considered in analyses of the association between hysterectomy and subsequent musculoskeletal health.

10.3 Specific objectives of the chapter

The specific objectives to be addressed in this chapter are:

i. to examine whether hysterectomy is associated with indicators of subsequent musculoskeletal health
ii. to examine whether the association between hysterectomy and musculoskeletal health differs by oophorectomy status, reason for and route of operation, age at hysterectomy and menopausal status at time of hysterectomy
iii. to examine whether the association between hysterectomy and subsequent musculoskeletal health is independent of factors which predict musculoskeletal health outcomes in middle-age and hysterectomy risk and where available, measures of pre-hysterectomy musculoskeletal health

10.4 Methods

10.4.1 Main outcome variables

Measures of physical performance (grip strength, chair rise time, standing balance time and a summary measure of overall functional performance) and functional limitation (difficulty walking, climbing stairs and gripping objects) as proxy measures of musculoskeletal health at age 53 years.

10.4.2 Main explanatory variable

Hysterectomy status

10.4.3 Covariates

Lifetime SEP (father's occupational class in childhood, maternal education level, own occupational class in adulthood and educational level attained), age at menarche, age at first birth, BMI at ages 26 and 53 years, exercise levels at ages 36 years, history of HRT use at age 53 years, functional limitation at age 43 years

10.4.4 Exclusions

Women whose hysterectomy or oophorectomy was performed at or after age 53 years (given these analyses aimed to test the association between hysterectomy and *subsequent* musculoskeletal health).

10.4.5 Description and ascertainment of outcome variables

10.4.5.1 Summary

Two sets of musculoskeletal health measures at age 53 years were available for analysis in the NSHD:

(1) maximal performance measures – grip strength, chair rise time and standing balance time

(2) self-reported functional limitations – difficulty walking, climbing stairs and gripping objects

These are all proxy measures of musculoskeletal health. Grip strength is a simple isometric test of upper body muscle strength whereas chair rise and standing balance times are measures of lower body muscle strength, neuromuscular speed and control and appropriate processing by the central nervous system.[447] These three measures of physical performance have all been found in other studies to significantly predict frailty, disability, quality of life and mortality in later life.[442;444-446;455-460]

Measures of functional limitation were also included as outcomes because they are markers of global musculoskeletal health, demonstrating how the physical performance tests with which they are associated translate into effects on people's daily lives. Further, they allow inclusion of women excluded from analyses of the three main physical performance outcomes because they were unable to do the tests due to disability and, unlike the physical performance tests, these outcomes were also measured at age 43 years allowing pre-hysterectomy levels to be adjusted for in subgroup analyses.

All outcomes were measured during the home visit at age 53 years. At this visit trained nurses conducted the three tests of physical performance designed to elicit maximal performance using standardised protocols as described by Kuh and colleagues[447] and repeated here.

10.4.5.2 Grip strength

Voluntary muscle strength (i.e. grip strength) was measured isometrically using an electronic handgrip dynamometer. The dynamometers were calibrated at the start using a back-loading rig; they are accurate, linear and stable to ± 0.5 kg. There were 2 sizes of handle for the transducer to accommodate different hand sizes. Each nurse was taught to give strong verbal encouragement to elicit maximal performance from the participants. Two values were recorded for each hand and the highest used in analyses. The intra-subject re-test variability for maximal voluntary tests of strength in those unused to such measurements is approximately ± 9%.[461]

10.4.5.3 Standing balance time

Standing balance time was measured, using a stopwatch, as the longest time, up to a maximum of 30 seconds, for which participants could maintain a one-legged stance in a standard position. Participants were asked to remove their shoes and then while standing, fold their arms and raise their preferred foot a few inches off the ground by bending the knee sufficiently. This was done first with eyes open and then with eyes closed. Most participants completed 30 seconds with their eyes open, so scores with eyes closed were used to avoid a ceiling effect. The distribution of these times was positively skewed and so they were normalised using a natural logarithm transformation.

10.4.5.4 Chair rise time

Chair rise time was measured, using a stopwatch, as the time taken to rise from a sitting to a standing position with straight back and legs and then sit down again ten complete times. Participants removed their shoes and sat in an armless straight-backed hard chair of normal height with a horizontal flat seat. In order for high scores to indicate good performance as for the other two tests the reciprocal of the time taken (multiplied by 100) was used.

10.4.5.5 Overall functional performance

In addition to considering the three physical performance measures as separate outcomes they have also been used to derive a summary measure of overall functional performance by Guralnik and colleagues.[449] This was considered as a fourth performance outcome in this chapter. To create this summary measure, outcomes of each of the three performance tests were rescaled to a 0 to 1 scale. The re-scaling was done separately for men and women. Grip strength adjusted for body size was divided by the sex-specific 99th percentile value of adjusted grip strength (0.2838 kg/cm for women). Women who had a grip strength greater than 0.2838 kg/cm were assigned a score of 1 and those unable to do the test assigned a score of 0. Balance was rescaled by dividing the total time the stand with eyes closed was held by the maximum possible time, 30 seconds. People unable to hold the position for even a small amount of time were assigned a score of 0. Rescaled chair rise time was calculated using the equation 1-(chair rise time/48.0 seconds), where 48.0 was the 99th percentile of time. People unable to rise from a chair 10 times and those taking longer than 48.0 seconds were assigned a score of 0. The three rescaled performance scores were summed to create a normally distributed aggregate functional performance score with a range of 0 to 3. The main benefits of this measure were that it provided a useful summary of overall physical performance and allowed inclusion of women visited at age 53 years who were unable to complete the physical performance tests.

As in analyses of these outcome data by other researchers,[450] all four measures described above were included in analyses as continuous measures so that the full range of function could be studied, to provide extra statistical power and because there is a linear increase in disability across these scores and no agreed clinical thresholds. The three physical performance measures were considered as three separate outcomes in addition to the composite score because, as detailed above, they all measure different aspects of musculoskeletal health, a fact highlighted by the finding that the correlation coefficients between the three variables were all less than 0.12.

10.4.5.6 Functional limitations

The three measures of functional limitation were ascertained by nurses during the home visit at age 53 years who asked study participants whether, because of long-term health problems, they had difficulty walking for quarter of a mile (400 yards) on the level, walking up and down a flight of 12 stairs in a normal manner and, holding something heavy such as full kettle or removing a tightly sealed lid from a jar. These were coded as binary variables (yes vs. no).

10.4.6 Ascertainment of covariates

To ensure comparability between models of different musculoskeletal outcomes all factors identified as influencing risk of at least one musculoskeletal outcome which in addition have been found to predict risk of hysterectomy were included in adjusted analyses.

Details of the ascertainment of the four measures of SEP used in analyses were provided in chapter 4, of ages at menarche and first birth in chapter 6, of BMI at ages 26 and 53 years in chapter 5 and of exercise level and HRT use in the previous chapter. Measures of functional limitations at age 43 years equivalent to the measures at age 53 years were ascertained during home visits at 43 years. During this visit participants were required to self-complete a screening questionnaire based on an OPCS disability survey which asked whether because of physical or mental health problems they had difficulty: walking for quarter of a mile; going up or down stairs; and using their hands to hold, grip or turn things.[462]

BMI at ages 26 and 53 years were included as continuous variables, age at menarche and age at first birth were both grouped into 4 categories (age at menarche: ≤11; 12; 13; ≥14 years, age at first birth: ≤20; 21-25; 26-30; >30 years). Father's and own occupational class and maternal education were also grouped into 4 categories, educational level attained into 5 and HRT use and exercise level into 3, as described in the previous chapter. The three functional limitation variables at age 43 years were coded as binary variables.

10.4.7 Analyses

10.4.7.1 Analyses to address objective (i) – unadjusted associations

A comparison of mean values of the four measures of physical performance (chair rise time, grip strength, standing balance time and overall functional performance) at age 53 years by prior hysterectomy status was performed using one-way analysis of variance and linear regression models. Checks to ensure that standard deviations were similar and the four measures were approximately normally distributed in each category of hysterectomy status by plotting histograms confirmed that it was appropriate to use this method of analysis. Chi-squared tests and logistic regression models were then used to compare the proportion of people with each one of the three functional limitations by prior hysterectomy status.

10.4.7.2 Analyses to address objective (ii) – characteristics of hysterectomy

The above analyses were rerun with prior hysterectomy status categorised by each of the characteristics of hysterectomy described in chapter 8.

Using likelihood ratio tests, regression models of the association between each characteristic of hysterectomy and subsequent musculoskeletal health were compared to a regression model in which all hysterectomies were grouped together. These comparisons were performed for each of the seven outcomes with linear regression models used for performance measures and logistic regression models used for functional limitations. Women who had undergone an oophorectomy only were excluded from all analyses except those assessing the difference in associations by oophorectomy status.

10.4.7.3 Analyses to address objective (iii) – adjusted associations

Using multiple regression or logistic regression models (as appropriate for the outcome) the association between hysterectomy status and each outcome at age 53 years was adjusted in separate models for: age at menarche; age at first birth; lifetime SEP (father's occupational class in childhood, maternal education, educational level attained and own occupational class in adulthood); exercise levels at age 36 years; BMI at ages 26 and 53 years; and history of HRT use. Where appropriate likelihood ratio tests were performed to examine whether variables were most appropriate to be entered as linear or categorical terms.

Further likelihood ratio tests were performed to test for interaction between HRT use and hysterectomy status given that HRT use may modify the effect of hysterectomy on the outcomes rather than confound it. When examining the three functional limitation outcomes at age 53 years a further set of adjustments were made for the equivalent functional limitation at age 43 years. As these were meant to be a measure of pre-hysterectomy functional limitation, models including functional limitation at age 43 years excluded not only women whose hysterectomy or oophorectomy occurred at or after age 53 years but also those performed at or before age 43 years.

In a final set of models including only those women with complete data on hysterectomy status and all other covariates identified as important, the association between hysterectomy status and each musculoskeletal health outcome at age 53 years was individually adjusted for each set of covariates. All covariates were then adjusted for in a final model. All of the variables which likelihood ratio tests suggested improved the fit of the model were included in these analyses.

To maximise power the above analyses were first run with hysterectomy status categorised as no hysterectomy or oophorectomy vs. hysterectomy with or without oophorectomy. The analyses were then rerun with hysterectomy categorised by any characteristic identified as significant in analyses to address objective (ii). Women who had had an oophorectomy only were excluded from all these models as the regression coefficients estimated for the oophorectomy only group, as in analyses in the previous chapter, were unstable.

10.5 Results

10.5.1 Results from analyses to address objective (i) - unadjusted associations

Women who had previously had a hysterectomy or oophorectomy had poorer physical performance and greater odds of experiencing functional limitations at age 53 years than women who had not undergone a hysterectomy or oophorectomy, tables 10.1 and 10.2. However, these differences by hysterectomy status were small and only significant for standing balance time and having difficulty with stairs and holding something heavy or removing a stiff lid.

10.5.2 Results from analyses to address objective (ii) - characteristics of hysterectomy

There was some variation in each of the main outcomes by each characteristic of hysterectomy. However, except for age at hysterectomy, there was no evidence from likelihood ratio tests that categorising hysterectomy by any one of the characteristics was significantly different from grouping all hysterectomies together (see appendices 8 and 9).

Results from analyses by age at hysterectomy showed that women who had a hysterectomy before age 40 years had significantly poorer physical performance and greater odds of functional limitation at age 53 years than women who had not had a hysterectomy or oophorectomy or who had a hysterectomy at a later age, tables 10.3 and 10.4. For example, women who had a hysterectomy before age 40 years had a mean grip strength at age 53 years 2.37kg lower and, odds of suffering from difficulties with stairs and with holding something heavy or removing a stiff lid over twice as high as those women who had not had a hysterectomy or oophorectomy. Meanwhile women who had a hysterectomy between ages 45 and 49 years had a mean grip strength at age 53 years 0.71kg lower and only slightly increased odds of suffering from difficulties with stairs and with holding something heavy or removing a stiff lid compared to women who had not had a hysterectomy or oophorectomy.

10.5.3 Results from analyses to address objective (iii) - adjusted associations

In analyses grouping all hysterectomies together, the association between hysterectomy status and standing balance time attenuated after adjustment for lifetime SEP, BMI at ages 26 and 53 years and age at first birth. Conversely adjustment for HRT use increased the difference in mean standing balance time between the hysterectomy and no hysterectomy groups, table 10.5. Associations between hysterectomy and the three other measures of physical performance, which were non-significant in unadjusted analyses, did not become significant after adjustment for any of the potential confounders (results not shown).

The associations between hysterectomy status and difficulty with stairs and with holding something heavy attenuated after adjustment for lifetime SEP, BMI at ages 26 and 53 years, age at first birth and HRT use, table 10.5. Adjustment for age at menarche, exercise levels and limitation at age 43 years had very small effects suggesting that these variables did not confound the main associations of interest. The association between hysterectomy and difficulty holding something heavy remained significant after adjustment for each set of potential confounders. In none of these analyses was there evidence of interaction.

As there was significant variation in association by age at hysterectomy, the associations between hysterectomy and each outcome by age at hysterectomy adjusted for each set of potential confounders were examined. In these analyses age at hysterectomy was grouped into four categories (no hysterectomy or oophorectomy; hysterectomy at < 40; 40-49 years; ≥50 years) instead of five as prior analyses suggested no difference between groups aged 40-44 and 45-49 years. The size and level of significance of the association between having a hysterectomy before age 40 years and all four physical performance measures, especially grip strength, attenuated after adjustment for age at first birth and for lifetime SEP, table 10.6. Adjustment for exercise levels, age at menarche, BMI and HRT use had only small effects on mean differences in outcomes between the no hysterectomy and hysterectomy before age 40 years groups and mean differences which were significant in unadjusted analyses remained significant in analyses adjusted for these variables.

The effect of having a hysterectomy before age 40 years on the odds of all three measures of functional limitation at age 53 years attenuated after adjustment for age at first birth, lifetime SEP, BMI and HRT use, table 10.7. While individual adjustment for each set of factors attenuated the size of the associations between hysterectomy before age 40 years and difficulty walking to the point of non-significance, the effect of having a hysterectomy before age 40 years on difficulties with stairs and with holding something heavy retained significance after these adjustments. Adjustments for functional limitation at age 43 years were not performed as the main group of interest (i.e. those women with a hysterectomy prior to age 40 years) would have been excluded from analyses.

When attempts were made to adjust simultaneously for all variables which appeared to have a confounding effect on the main associations it was necessary to restrict the sample to only those women with complete data on all these variables. When these restrictions were used the total N available for analysis fell to less than 820 and the estimates of unadjusted effect were different from the estimates in analyses presented suggesting that the exclusions had introduced bias and that the results from these fully adjusted models were not useful. As age at first birth and lifetime SEP appeared to be the most consistent confounders of the association between hysterectomy and all outcomes these variables were adjusted for together in a set of models. When the sample was restricted to those women with complete data on lifetime SEP and age at first birth, adjustment for the two sets of factors together attenuated the size of the associations between hysterectomy and each outcome by a greater amount than adjusting for either set of factors by themselves.

10.6 Discussion

10.6.1 Main findings

Overall, women in the NSHD who had undergone a hysterectomy or oophorectomy had poorer scores in tests of physical performance and higher odds of functional limitation at age 53 years than women who had not undergone a hysterectomy or oophorectomy however these differences were only significant in analyses of three out of the seven outcomes considered.

Timing of hysterectomy may be important in determining a woman's risk of poor musculoskeletal health at age 53 years. Women who had a hysterectomy before age 40 years were found to be at significantly greater risk of poor physical performance and had higher odds of functional limitation at age 53 years than women who had not undergone a hysterectomy or oophorectomy or who had a hysterectomy at a later age.

These associations were found to be at least partially explained by a range of factors from across life, most importantly age at first birth, lifetime SEP and BMI in adulthood.

10.6.2 Comparison with other studies

This is the first study, as far as we are aware, which has examined the effect of hysterectomy on musculoskeletal health outcomes other than bone density.

10.6.3 Explanation of findings

The effect of hysterectomy overall on musculoskeletal health by age 53 years appears to be small with results, although not conclusive because of the limits of the data, suggesting that most of the differences in outcome overall can probably be explained by common risk factors such as timing of childbirth, lifetime SEP and BMI which predict both musculoskeletal health and hysterectomy risk. Other common risk factors not examined could also potentially help explain the associations found including genetic factors, for example, there is evidence that the oestrogen receptor α gene is associated with hysterectomy risk[170] and also with musculoskeletal outcomes.[385;386]

The results provide no clear evidence of a pathway between hysterectomy and subsequent musculoskeletal health mediated by oestrogen exposure – while women who had undergone an oophorectomy only appeared to have poorer musculoskeletal health at age 53 years than other women, women who had had a hysterectomy with oophorectomy had better scores in tests of physical performance than women who had a hysterectomy with ovarian conservation.

The most significant finding of these analyses was the greater risk of poor musculoskeletal health in middle-age experienced by women who had a hysterectomy at a young age (i.e. before age 40 years). If any effect of hysterectomy on musculoskeletal health had developed as a direct result of the period of inactivity which is necessary while recovering from the operation it would have been expected that it would have been women who had hysterectomies at later ages, closest in time to the home visit at age 53 years, who would have had the poorest scores in tests of physical performance and the greatest levels of functional limitation at this time, not, as was found, the women who had hysterectomies at young ages.

The association between hysterectomy at a young age and poor musculoskeletal health could be explained by the existence of a time lag between hysterectomy and musculoskeletal health. If this time lag was sufficiently long it may be that only the women whose hysterectomies were performed before age 40 years have had sufficient time between their hysterectomy and outcome measurement for the effect to be seen yet. However, this seems unlikely and there is no obvious plausible pathway on which hysterectomy would take such a long time to affect musculoskeletal health.

It is also possible that there is something particularly harmful about having a hysterectomy at a young age. The implication of this would be that if the women whose hysterectomies were performed before age 40 years had had their procedures delayed to a later age their musculoskeletal health at age 53 years would have been no different to other women's, a finding of potential clinical importance. One way in which hysterectomy could be more damaging the earlier it is performed is through its effect on hormone exposure. If hysterectomy is associated with reductions in oestrogen and testosterone exposure, women exposed to these reductions at younger ages and further from the time that these reductions would have naturally occurred (i.e. with menopause) may be at higher risk of conditions influenced by such reductions. However, evidence that hysterectomy disrupts hormone exposure even if the ovaries are conserved is not fully consistent and requires further investigation.

Another possibility is that women who had hysterectomies at a young age had hysterectomies for different reasons to those performed later and that the conditions associated with hysterectomy at young ages share a common aetiology with poor musculoskeletal outcomes or, the conditions associated with hysterectomy at later ages share a common aetiology with favourable musculoskeletal outcomes. However, as shown in chapter 2 there is insufficient variation in reason for hysterectomy by age at operation for this to have driven the association and provide a full explanation.

One of the most likely explanations is that women who had hysterectomies earlier in life had higher levels of risk factors for poor musculoskeletal health than women who did not have a hysterectomy and than women who had hysterectomies at later ages. If this was the case these women can be expected to have experienced poorer musculoskeletal outcomes whatever age they had been when they had their hysterectomies. This explanation is supported by the attenuation in effect of young age at hysterectomy on all musculoskeletal outcomes seen after adjustment for potential confounders, most importantly, age at first birth and lifetime SEP. Women in the NSHD who had hysterectomies before age 40 years had younger ages at first birth and lower lifetime SEP than women who had hysterectomies at later ages - as shown in chapters 4 and 6 the effects of both SEP and young age at first birth on risk of hysterectomy were significant but attenuated with increasing age.

A further possibility is that hysterectomy especially at young ages is an indicator of early ageing, i.e. the premature onset of chronic health problems usually associated with old-age. It is possible that early age at hysterectomy is part of a complex of factors including subfertility, early onset of menopausal symptoms and HRT use which indicate premature ovarian ageing.[463] As there is thought to be a link between ovarian and general ageing[464] factors which indicate premature ovarian ageing could also be indicators of premature general ageing. If this were the case then early age at hysterectomy would not itself precipitate subsequent poor musculoskeletal health but would indicate women who had a higher risk of such health outcomes, which are usually associated with ageing, occurring. This however, is speculative and requires further investigation.

10.6.4 Limitations

In the previous chapter, a major strength of the analyses was that it was possible to adjust for a pre-hysterectomy level of the main outcome measure, BMI. Unfortunately the three main measures of physical performance used in this chapter's analyses were recorded for the first time at age 53 years and so it was not possible to adjust for pre-hysterectomy levels of these. It was thus not possible to test whether any differences in these three measures or in the composite summary score existed prior to hysterectomy or had developed since and possibly as a consequence of hysterectomy.

Without consideration of pre-hysterectomy measures of the outcome, especially if the level of the outcome at any one time of measurement is dependent on earlier levels, the possibility of reverse causality cannot be ruled out. There is evidence that women with physical disabilities may be more likely to undergo hysterectomy than other women partly because they more often undergo the procedure for contraceptive purposes in addition to using it as treatment for gynaecological conditions.[465] If this was the case in the NSHD, an association between hysterectomy and poor physical performance at age 53 years may have been seen because disability (which would result in poorer physical performance and greater levels of reporting of functional limitations) predicts hysterectomy. This is unlikely to be a major limitation in the NSHD as the number of women with severe physical disabilities was very low. Further, the associations between hysterectomy and functional limitations at age 53 years were not explained by functional limitations at age 43 years, pre-hysterectomy.

Women were excluded from analyses of the three physical performance measures if they were unable to attempt or complete the tests which measured these outcomes. This could have introduced bias especially if the women who could not perform the tests had a different prevalence of hysterectomy compared to women who could perform the tests. However, while the women unable to perform the tests had poorer general health, were more likely to be inactive and of lower SEP[447] than women who did complete the tests, they did not have a significantly different prevalence of hysterectomy (results not shown) and so any bias introduced is likely to have been minimal. This is supported by the results of analyses of the overall performance score which included women unable to do the tests and which produced results very similar to those from analyses of the three physical performance scores.

In unadjusted analyses women who had undergone an oophorectomy only appeared to have poorer physical performance and higher odds of functional limitation compared to women who had not had a hysterectomy or oophorectomy. However, due to the small number of women who had undergone oophorectomy only these analyses had low power. Low power was also a limitation of many of the analyses by characteristic of hysterectomy whereby variations in effect of hysterectomy by characteristic may have gone undetected. Excluding women who did not have complete data on a number of covariates limited the power of the multivariable analyses and also introduced bias.

As in the previous chapter, these analyses excluded women who had hysterectomies or oophorectomies at or after age 53 years in order to establish a clear temporal relationship between hysterectomy and subsequent health. It is thus not possible to test whether hysterectomies performed at later ages have a different effect on musculoskeletal health outcomes to those performed before age 53 years. However, as stated in the previous chapter as there was a downward trend in rates of hysterectomy being performed by age 53 years this is not a major limitation. Further, any effect of hysterectomy on musculoskeletal health appears to be restricted to hysterectomies performed earlier in adulthood rather than later.

It is possible that the associations were confounded by other factors not identified. It is also possible, as in the previous chapter, that some of the variables included were not sufficiently well defined for all confounding or modifying effects of these variables to be appropriately tested and adjusted for in analyses. Further, it may not have been appropriate to have adjusted for factors such as BMI and HRT use at age 53 years given they could have mediated rather than confounded the main associations of interest. However, neither of these variables had a large effect on the main associations of interest and age at first birth and lifetime SEP which came in time before both hysterectomy and outcome measurement had a much greater effect than these variables.

While all outcomes in this chapter can be considered as markers of musculoskeletal health the performance scores women achieve and the functional limitations they report are affected not only by the condition of the musculoskeletal system but also by mental health and the condition of other systems including the respiratory and cardiovascular systems. An effect of hysterectomy on the outcomes considered in this chapter may thus have been seen not because of an effect of hysterectomy on the musculoskeletal system but because of an effect of hysterectomy on the function of other systems which influence the measures of physical performance and functional limitation considered.

The measures of functional limitation considered were all self-reported, based on responses to questions which could be interpreted differently by different people. Further these outcomes were coded as binary variables. These subjective measures may thus not be sensitive enough to detect those women who have real problems in carrying out daily activities related to their musculoskeletal health at a particular age or whose limitations have persisted across time. However, the other outcomes considered in this chapter i.e. the measures of physical performance were measured by trained professionals on a continuous scale and so are not subject to this potential limitation.

All women in the NSHD who had not had a hysterectomy or oophorectomy were grouped together to form a comparison group. However, it may be that there are important differences in musculoskeletal health at age 53 years by menopausal status at this age.

Further work is required to examine whether differences in musculoskeletal health by menopausal status and timing of menopause exist in the NSHD.

It may be that declines in physical performance are a more important determinant of disability, frailty, quality of life and mortality in later life than absolute levels of performance. As physical performance has only been measured at one time point it has not been possible to assess whether hysterectomy results in rates of decline in performance any different to those seen in other women as they age. Further, as bone density has not been measured it has not been possible to test whether hysterectomy has any effect on this component of musculoskeletal health. This is despite the fact that there are more plausible reasons to expect associations to be found between hysterectomy and bone density than between hysterectomy and other measures of musculoskeletal health. With data from future data collections it will be possible to study the effect of hysterectomy on both rates of decline in physical performance and on bone density.

10.6.5 Strengths

A major strength of these analyses is that it has been possible to examine the effect of hysterectomy on a range of musculoskeletal outcomes. These were all measured prospectively, the majority by trained health professionals using standardised protocols. It has been possible to study associations between hysterectomy and musculoskeletal health outcomes and assess whether there are differences in effect by characteristic of hysterectomy which no previous researchers have examined.

As in the previous chapter, another major strength of these analyses is the wealth of information prospectively collected about the NSHD at time points across life which made it possible to adjust for a range of factors from across life which could confound the main associations of interest.

10.6.6 Conclusions and implications

Overall, effects of hysterectomy on musculoskeletal health in middle-age in the NSHD were small, appeared to be largely restricted to hysterectomies performed before age 40 years and were at least partially explained by common risk factors such as lifetime SEP and age at first birth. The most likely explanations of an association between hysterectomy at a young age and musculoskeletal health are that hysterectomy at a young age is a manifestation of early ageing and/or women who had hysterectomies at a young age possessed higher risk profiles for poor musculoskeletal health than other women. This suggests that women who have hysterectomies at young ages represent a group whom advice about the maintenance of good musculoskeletal health could be targeted.

All effects found in these analyses were small and whether they are clinically relevant is not yet known. As the cohort age and the incidence of clinical musculoskeletal outcomes such as osteoporosis, osteoarthritis and sarcopaenia increases it will be possible to identify whether these small differences do translate into differences in the incidence of clinically important outcomes and levels of disability.

Although there is no clear evidence that HRT use does protect women against declines in musculoskeletal health it is possible that there is an undetected protective effect. In cohorts of women younger than the NSHD the proportion of women using HRT is expected to be lower – younger women are likely to have been more greatly affected by the decline in popularity for prescribing HRT which resulted from the publication of findings from the Women's Health Initiative and other large randomised controlled trials.[466;467] This decline in use of HRT may result in greater differences in musculoskeletal outcomes by hysterectomy status being seen in cohorts younger than the NSHD.

Further research using data from the NSHD as the cohort ages and from other cohorts of different ages is necessary before definitive conclusions about the association between hysterectomy and musculoskeletal health can be made.

Table 10.1: Means and unadjusted differences in mean values of measures of physical performance by hysterectomy status in the NSHD

Hysterectomy status	Chair rises ([1/time(seconds)] x 100)			Grip strength (kg)			Standing balance ($\log_e$ (time(seconds)))			Overall performance score		
	N	Mean (SD)	Regression coefficient (95% CI)	N	Mean (SD)	Regression coefficient (95% CI)	N	Mean (SD)	Regression coefficient (95% CI)	N	Mean (SD)	Regression coefficient (95% CI)
No hyst.*	1055	5.06 (1.59)	0.00	1089	27.88 (7.80)	0.00	1060	1.54 (0.75)	0.00	1060	1.31 (0.37)	0.00
Hysterectomy†	293	4.94 (1.58)	-0.11 (-0.32, 0.09)	301	27.39 (8.32)	-0.49 (-1.50, 0.52)	296	1.44 (0.75)	-0.10 (-0.20, -0.01)	297	1.27 (0.37)	-0.04 (-0.09, 0.01)
Oophorectomy only♦	18	5.14 (1.77)	0.08 (-0.66, 0.82)	20	26.42 (8.02)	-1.46 (-4.96, 2.05)	20	1.14 (0.86)	-0.41 (-0.74, -0.08)	20	1.21 (0.39)	-0.10 (-0.26, 0.06)
Total	1366	5.03 (1.59)		1410	27.75 (7.92)		1376	1.51 (0.75)		1377	1.30 (0.37)	
p-value (F test)			0.54			0.48			0.008			0.16

Table 10.2: Unadjusted associations between hysterectomy status and measures of functional limitation at age 53 years in the NSHD

Hysterectomy status	Total N	Difficulties walking 400 yards on level		Difficulties with stairs		Difficulties holding something heavy or removing a stiff lid	
		Yes N (%)	Odds Ratio (95% CI)	Yes N (%)	Odds Ratio (95% CI)	Yes N (%)	Odds Ratio (95% CI)
No hysterectomy*	1148	130 (11.3)	1.00	197 (17.2)	1.00	235 (20.5)	1.00
Hysterectomy†	317	41 (12.9)	1.16 (0.80, 1.69)	69 (21.8)	1.34 (0.99, 1.83)	91 (28.7)	1.56 (1.18, 2.07)
Oophorectomy only♦	20	3 (15.0)	1.38 (0.40, 4.78)	8 (40.0)	3.22 (1.30, 7.98)	6 (30.0)	1.67 (0.63, 4.38)
Total	1485	174 (11.7)		274 (18.5)		332 (22.4)	
p-value (χ^2 test)			0.66		0.01		0.01

* No hysterectomy or oophorectomy
† with or without oophorectomy
♦ bilateral or unilateral

Table 10.3: Unadjusted differences in mean values of measures of physical performance by age at hysterectomy in the NSHD

Age at hysterectomy (years)	Regression coefficient (95% CI) Chair rises ([1/time(seconds)] x 100) (N=1348)	Grip strength (kg) (N=1390)	Standing balance ($\log_e$ (time(seconds))) (N=1356)	Overall performance score (N=1357)
No hysterectomy or oophorectomy	0.00	0.00	0.00	0.00
< 40	-0.42 (-0.78, -0.06)**	-2.37 (-4.17, -0.58)**	-0.15 (-0.32, 0.02)	-0.13 (-0.22, -0.05)**
40 - 44	0.11 (-0.26, 0.47)	-0.27 (-2.06, 1.53)	-0.15 (-0.33, 0.02)	-0.02 (-0.11, 0.07)
45 - 49	-0.12 (-0.45, 0.22)	-0.71 (-2.35, 0.92)	-0.06 (-0.21, 0.10)	-0.03 (-0.11, 0.04)
≥ 50	0.08 (-0.40, 0.55)	3.12 (0.71, 5.52)	-0.04 (-0.27, 0.18)	0.11 (-0.01, 0.22)
p-value	*0.17*	*0.003*	*0.74*	*0.007*

Table 10.4: Unadjusted associations between age at hysterectomy and measures of functional limitation at age 53 years in the NSHD

Age at hysterectomy (years)	Total N	Difficulties walking 400 yards on level: Yes N (%)	Odds Ratio (95% CI)	Difficulties with stairs: Yes N (%)	Odds Ratio (95% CI)	Difficulties holding something heavy or removing a stiff lid: Yes N (%)	Odds Ratio (95% CI)
No hysterectomy or oophorectomy	1148	130 (11.3)	1.00	197 (17.2)	1.00	235 (20.5)	1.00
< 40	88	16 (18.2)	1.74 (0.98, 3.08)	27 (30.7)	2.14 (1.32, 3.45)**	31 (35.2)	2.11 (1.33, 3.35)**
40 - 44	83	6 (7.2)	0.61 (0.26, 1.43)	16 (19.3)	1.15 (0.65, 2.03)	19 (22.9)	1.15 (0.68, 1.96)
45 - 49	100	14 (14.0)	1.27 (0.70, 2.31)	19 (19.0)	1.13 (0.67, 1.91)	27 (27.0)	1.44 (0.90, 2.29)
≥ 50	46	5 (10.9)	0.95 (0.37, 2.46)	7 (15.2)	0.87 (0.38, 1.97)	14 (30.4)	1.70 (0.89, 3.24)
p-value			*0.17*		*0.12*		*0.33*

** $p < 0.05$

Note: p-values from likelihood ratio tests comparing models with categorisations of hysterectomy shown with a model in which all hysterectomies were grouped together (women with oophorectomy only excluded)

Table 10.5: Comparison of musculoskeletal health outcomes by hysterectomy status adjusted for individual sets of variables in the NSHD

Adjusted for:	Standing balance time Regression coefficient (Mean difference (log_e (time(seconds)))) (95% CI)	p-value	Difficulties with stairs Odds Ratio (95% CI)	p-value	Difficulties holding something heavy or removing a stiff lid Odds Ratio (95% CI)	p-value
Age at menarche	N=1105		N=1192			
Unadjusted	-0.09 (-0.19, 0.02)	0.11	1.20 (0.85, 1.70)	0.31	1.63 (1.19, 2.23)	0.002
Adjusted	-0.08 (-0.19, 0.02)	0.12	1.18 (0.83, 1.67)	0.36	1.60 (1.17, 2.19)	0.003
Age at first birth	N=1197		N=1286			
Unadjusted	-0.07 (-0.17, 0.03)	0.16	1.37 (0.99, 1.90)	0.06	1.45 (1.08, 1.94)	0.01
Adjusted	-0.05 (-0.14, 0.05)	0.37	1.31 (0.95, 1.82)	0.10	1.38 (1.03, 1.86)	0.03
Lifetime SEP	N=1104		N=1187			
Unadjusted	-0.06 (-0.17, 0.04)	0.24	1.28 (0.90, 1.82)	0.17	1.48 (1.07, 2.04)	0.02
Adjusted	-0.03 (-0.13, 0.08)	0.59	1.21 (0.85, 1.72)	0.29	1.44 (1.04, 1.99)	0.03
Exercise at age 36 years	N=1240		N=1338			
Unadjusted	-0.11 (0.21, -0.01)	0.03	1.32 (0.96, 1.82)	0.09	1.60 (1.20, 2.14)	0.002
Adjusted	-0.11 (-0.21, -0.01)	0.03	1.30 (0.94, 1.80)	0.11	1.59 (1.19, 2.14)	0.002
BMI at 26 and 53 years	N=1221		N=1305			
Unadjusted	-0.11 (-0.21, -0.01)	0.03	1.38 (1.00, 1.90)	0.05	1.64 (1.22, 2.20)	0.001
Adjusted	-0.08 (-0.17, 0.02)	0.12	1.27 (0.91, 1.78)	0.16	1.61 (1.19, 2.16)	0.002
HRT use at age 53 years	N=1356		N=1465			
Unadjusted	-0.10 (-0.23, -0.01)	0.04	1.34 (0.99, 1.83)	0.06	1.56 (1.18, 2.07)	0.002
Adjusted	-0.13 (-0.23, -0.03)	0.01	1.28 (0.93, 1.78)	0.13	1.37 (1.02, 1.85)	0.04
Same limitation at age 43 years			N=1234		N=1242	
Unadjusted	-		1.05 (0.68, 1.63)	0.83	1.33 (0.90, 1.96)	0.15
Adjusted	-		1.06 (0.67, 1.67)	0.82	1.33 (0.90, 1.97)	0.15

Baseline group = No hysterectomy or oophorectomy
Exposure group = Hysterectomy with or without oophorectomy
Women with oophorectomy only not included in analyses

Table 10.6: Differences in mean values of measures of physical performance by age at hysterectomy adjusted for individual sets of variables in the NSHD

Adjusted for:	Regression coefficient (95% CI) Chair rises ([1/time(seconds)] x 100)	p-value	Grip strength (kg)	p-value	Standing balance ($\log_e$ (time(seconds)))	p-value	Overall performance score	p-value
Age at menarche	N=1095		N=1133		N=1105		N=1104	
Unadjusted No hysterectomy*	0.00	0.30	0.00	0.003	0.00	0.27	0.00	0.003
Hysterectomy at age (yrs): <40	-0.44 (-0.84, -0.03)		-2.58 (-4.63, -0.54)		-0.16 (-0.34, 0.03)		-0.15 (-0.24, -0.05)	
40-49	-0.01 (-0.29, 0.28)		-0.39, (-1.80, 1.02)		-0.08 (-0.21, 0.05)		-0.02 (-0.09, 0.05)	
≥ 50	-0.003 (-0.55, 0.55)		3.91 (1.09, 6.73)		0.03 (-0.23, 0.28)		0.13 (-0.001, 0.26)	
Adjusted No hysterectomy*	0.00	0.21	0.00	0.005	0.00	0.29	0.00	0.004
Hysterectomy at age (yrs): <40	-0.44 (-0.84, -0.03)		-2.33 (-4.37, -0.29)		-0.15 (-0.34, 0.03)		-0.14 (-0.24, -0.05)	
40-49	-0.01 (-0.29, 0.28)		-0.23 (-1.64, 1.17)		-0.08 (-0.21, 0.06)		-0.02 (-0.08, 0.05)	
≥ 50	-0.003 (-0.55, 0.55)		3.89 (1.08, 6.70)		0.02 (-0.23, 0.28)		0.13 (-0.001, 0.26)	
Age at first birth	N=1189		N=1223		N=1197		N=1191	
Unadjusted No hysterectomy*	0.00	0.12	0.00	0.004	0.00	0.37	0.00	0.002
Hysterectomy at age (yrs): <40	-0.45 (-0.81, -0.08)		-2.13 (-4.02, -0.25)		-0.14 (-0.31, 0.03)		-0.14 (-0.22, -0.05)	
40-49	-0.06 (-0.32, 0.20)		-0.42 (-1.74, 0.90)		-0.06 (-0.18, 0.07)		-0.03 (-0.09, 0.03)	
≥ 50	0.06 (-0.42, 0.54)		3.42 (0.92, 5.93)		0.002 (-0.23, 0.23)		0.11 (-0.004, 0.23)	
Adjusted No hysterectomy*	0.00	0.19	0.00	0.01	0.00	0.73	0.00	0.006
Hysterectomy at age (yrs): <40	-0.41 (-0.78, 0.04)		-1.85 (-3.75, 0.05)		-0.09 (-0.26, 0.09)		-0.11 (-0.20, -0.03)	
40-49	-0.05 (-0.31, 0.21)		-0.38 (-1.70, 0.94)		-0.04 (-0.17, 0.08)		-0.03 (-0.09, 0.03)	
≥ 50	0.07 (-0.41, 0.55)		3.50 (0.99, 6.00)		0.01 (-0.22, 0.24)		0.12 (0.002, 0.23)	
Lifetime SEP	N=1103		N=1133		N=1104		N=1101	
Unadjusted No hysterectomy*	0.00	0.17	0.00	0.06	0.00	0.71	0.00	0.02
Hysterectomy at age (yrs): <40	-0.46 (-0.88, -0.04)		-1.62 (-3.72, 0.47)		-0.07 (-0.19, 0.19)		-0.13 (-0.22, -0.04)	
40-49	0.01 (-0.28, 0.29)		-0.25 (-1.68, 1.17)		-0.07 (-0.20, 0.07)		-0.01 (-0.08, 0.05)	
≥ 50	0.11 (-0.43, 0.65)		3.05 (0.26, 5.83)		-0.05 (-0.31, 0.20)		0.10 (-0.03, 0.23)	
Adjusted No hysterectomy*	0.00	0.10	0.00	0.06	0.00	0.92	0.00	0.04
Hysterectomy at age (yrs): <40	-0.40 (-0.82, 0.01)		-1.39 (-3.49, 0.71)		-0.002 (-0.19, 0.19)		-0.10 (-0.19, -0.01)	
40-49	0.03 (-0.25, 0.31)		-0.24 (-1.66, 1.19)		-0.05 (-0.18, 0.08)		-0.004 (-0.07, 0.06)	
≥ 50	0.19 (-0.35, 0.73)		3.23 (0.45, 6.02)		-0.01 (-0.26, 0.24)		0.12 (-0.01, 0.25)	

* No hysterectomy or oophorectomy

Table 10.6 continued: Differences in mean values of measures of physical performance by age at hysterectomy adjusted for individual sets of variables in the NSHD

Adjusted for:	Regression coefficient (95% CI) Chair rises ([1/time(seconds)] x 100)	p-value	Grip strength (kg)	p-value	Standing balance (log_e (time(seconds)))	p-value	Overall performance score	p-value
Exercise at age 36 years	N=1232		N=1267		N=1240		N=1241	
Unadjusted No hysterectomy*	0.00	0.19	0.00	0.001	0.00	0.13	0.00	0.002
Hysterectomy at age (yrs): <40	-0.42 (-0.79, -0.04)		-2.83 (-4.70, -0.97)		-0.15 (-0.32, 0.03)		-0.15 (-0.24, -0.06)	
40-49	-0.03 (-0.29, 0.23)		-0.78 (-2.06, 0.51)		-0.12 (-0.24, 0.01)		-0.04 (-0.10, 0.02)	
≥ 50	-0.05 (-0.53, 0.44)		2.82 (0.38, 5.26)		-0.04 (-0.27, 0.19)		0.09 (-0.02, 0.21)	
Adjusted No hysterectomy*	0.00	0.18	0.00	0.001	0.00	0.14	0.00	0.001
Hysterectomy at age (yrs): <40	-0.42 (-0.79, -0.05)		-2.86 (-4.72, -0.99)		-0.15 (-0.32, 0.02)		-0.15 (-0.23, -0.06)	
40-49	-0.02 (-0.28, 0.24)		-0.74 (-2.03, 0.53)		-0.11 (-0.24, 0.01)		-0.04 (-0.10, 0.02)	
≥ 50	-0.02 (-0.49, 0.46)		2.88 (0.45, 5.31)		-0.03 (-0.25, 0.20)		0.10 (-0.01, 0.22)	
BMI at ages 26 and 53 years	N=1210		N=1243		N=1221		N=1220	
Unadjusted No hysterectomy*	0.00	0.13	0.00	0.001	0.00	0.13	0.00	0.0003
Hysterectomy at age (yrs): <40	-0.45 (-0.83, -0.08)		-2.97 (-4.84, -1.10)		-0.16 (-0.33, 0.02)		-0.16 (-0.25, -0.08)	
40-49	-0.04 (-0.31, 0.22)		-0.78 (-2.08, 0.52)		-0.11 (-0.23, 0.02)		-0.05 (-0.11, 0.01)	
≥ 50	-0.05 (-0.53, 0.44)		2.85 (0.40, 5.31)		-0.04 (-0.27, 0.19)		0.09 (-0.03, 0.20)	
Adjusted No hysterectomy*	0.00	0.23	0.00	0.001	0.00	0.40	0.00	0.002
Hysterectomy at age (yrs): <40	-0.38 (-0.75, -0.01)		-2.86 (-4.73, -0.98)		-0.11 (-0.28, 0.06)		-0.14 (-0.22, -0.05)	
40-49	0.004 (-0.26, 0.27)		-0.74 (-2.04, 0.56)		-0.08 (-0.20, 0.04)		-0.04 (-0.10, 0.02)	
≥ 50	0.02 (-0.46, 0.50)		2.94 (0.49, 5.40)		-0.01 (0.23, 0.21)		0.10 (-0.01, 0.22)	
HRT use at age 53 years	N=1348		N=1390		N=1356		N=1357	
Unadjusted No hysterectomy*	0.00	0.20	0.00	0.002	0.00	0.17	0.00	0.002
Hysterectomy at age (yrs): <40	-0.42 (-0.78, -0.06)		-2.37 (-4.17, -0.73)		-0.15 (-0.32, 0.02)		-0.13 (-0.22, -0.05)	
40-49	-0.02 (-0.28, 0.24)		-0.51 (-1.76, 0.74)		-0.10 (-0.22, 0.02)		-0.03 (-0.09, 0.03)	
≥ 50	0.08 (-0.40, 0.55)		3.12 (0.71, 5.52)		-0.04 (-0.27, 0.18)		0.11 (-0.01, 0.22)	
Adjusted No hysterectomy*	0.00	0.12	0.00	0.002	0.00	0.09	0.00	0.001
Hysterectomy at age (yrs): <40	-0.45 (-0.81, -0.08)		-2.55 (-4.38, -0.73)		-0.17 (-0.34, 0.0002)		-0.16 (-0.24, -0.07)	
40-49	-0.06 (-0.32, 0.21)		-0.73 (-2.02, 0.56)		-0.12 (-0.25, 0.005)		-0.05 (-0.11, 0.01)	
≥ 50	0.03 (-0.46, 0.51)		2.82 (0.39, 5.26)		-0.07 (-0.30, 0.16)		0.08 (-0.04, 0.19)	

* No hysterectomy or oophorectomy

Table 10.7: Associations between hysterectomy and measures of functional limitation by age at hysterectomy adjusted for individual sets of variables in the NSHD

Adjusted for:		Odds ratio (95% CI)					
		Difficulties walking 400 yards on level	p-value	Difficulties with stairs	p-value	Difficulties holding something heavy or removing a stiff lid	p-value
Age at menarche (N=1192)							
Unadjusted	No hysterectomy*	1.00	0.57	1.00	0.04	1.00	0.01
Hysterectomy at age (yrs):	<40	1.55 (0.81, 2.97)		2.09 (1.23, 3.55)		2.29 (1.38, 3.81)	
	40-49	0.86 (0.49, 1.52)		0.99 (0.63, 1.56)		1.32 (0.88, 1.98)	
	≥ 50	0.98 (0.34, 2.83)		0.60 (0.21, 1.72)		1.82 (0.87, 3.77)	
Adjusted	No hysterectomy*	1.00	0.58	1.00	0.05	1.00	0.01
Hysterectomy at age (yrs):	<40	1.52 (0.79, 2.92)		2.03 (1.19, 3.46)		2.23 (1.34, 3.71)	
	40-49	0.85 (0.48, 1.50)		0.97 (0.62, 1.54)		1.30 (0.86, 1.95)	
	≥ 50	0.99 (0.34, 2.85)		0.60 (0.21, 1.73)		1.83 (0.88, 3.80)	
Age at first birth (N=1286)							
Unadjusted	No hysterectomy*	1.00	0.19	1.00	0.02	1.00	0.04
Hysterectomy at age (yrs):	<40	1.98 (1.11, 3.54)		2.19 (1.33, 3.61)		1.90 (1.17, 3.07)	
	40-49	1.02 (0.61, 1.71)		1.19 (0.79, 1.81)		1.23 (0.84, 1.80)	
	≥ 50	1.05 (0.40, 2.71)		0.79 (0.33, 1.90)		1.54 (0.79, 2.99)	
Adjusted	No hysterectomy*	1.00	0.43	1.00	0.06	1.00	0.12
Hysterectomy at age (yrs):	<40	1.67 (0.93, 3.02)		1.99 (1.20, 3.30)		1.70 (1.05, 2.77)	
	40-49	0.99 (0.59, 1.66)		1.17 (0.77, 1.78)		1.21 (0.83, 1.76)	
	≥ 50	1.00 (0.38, 2.60)		0.77 (0.32, 1.85)		1.50 (0.77, 2.93)	
Lifetime SEP (N=1187)							
Unadjusted	No hysterectomy*	1.00	0.37	1.00	0.15	1.00	0.08
Hysterectomy at age (yrs):	<40	1.83 (0.95, 3.54)		1.90 (1.09, 3.32)		1.81 (1.06, 3.11)	
	40-49	1.05 (0.60, 1.84)		1.16 (0.74, 1.81)		1.28 (0.84, 1.93)	
	≥ 50	1.35 (0.52, 3.56)		0.77 (0.30, 2.02)		1.75 (0.85, 3.61)	
Adjusted	No hysterectomy*	1.00	0.69	1.00	0.31	1.00	0.11
Hysterectomy at age (yrs):	<40	1.53 (0.78, 2.99)		1.73 (0.98, 3.03)		1.74 (1.01, 3.01)	
	40-49	1.01 (0.57, 1.78)		1.13 (0.72, 1.77)		1.24 (0.82, 1.88)	
	≥ 50	1.12 (0.42, 3.01)		0.70 (0.27, 1.84)		1.72 (0.83, 3.59)	

* No hysterectomy or oophorectomy

Table 10.7 continued: Associations between hysterectomy and measures of functional limitation by age at hysterectomy adjusted for individual sets of variables in the NSHD

Adjusted for:		Odds ratio (95% CI) Difficulties walking 400 yards on level	p-value	Difficulties with stairs	p-value	Difficulties holding something heavy or removing a stiff lid	p-value
Exercise at age 36 years (N=1338)							
Unadjusted	No hysterectomy	1.00	0.18	1.00	0.03	1.00	0.01
Hysterectomy at age (yrs):	<40	1.94 (1.09, 3.47)		2.16 (1.31, 3.57)		2.18 (1.35, 3.52)	
	40-49	0.91 (0.54, 1.54)		1.14 (0.75, 1.72)		1.37 (0.94, 1.98)	
	≥ 50	1.00 (0.38, 2.57)		0.75 (0.31, 1.81)		1.61 (0.83, 3.12)	
Adjusted	No hysterectomy	1.00	0.18	1.00	0.03	1.00	0.01
Hysterectomy at age (yrs):	<40	1.95 (1.08, 3.50)		2.17 (1.31, 3.59)		2.18 (1.35, 3.53)	
	40-49	0.88 (0.52, 1.50)		1.12 (0.74, 1.69)		1.36 (0.94, 1.97)	
	≥ 50	0.97 (0.37, 2.54)		0.74 (0.31, 1.78)		1.58 (0.81, 3.08)	
BMI at ages 26 and 53 years (N=1305)							
Unadjusted	No hysterectomy	1.00	0.21	1.00	0.02	1.00	0.005
Hysterectomy at age (yrs):	<40	1.95 (1.08, 3.54)		2.28 (1.38, 3.77)		2.24 (1.38, 3.62)	
	40-49	0.95 (0.55, 1.62)		1.17 (0.77, 1.78)		1.39 (0.95, 2.02)	
	≥ 50	1.08 (0.42, 2.81)		0.79 (0.33, 1.91)		1.65 (0.85, 3.21)	
Adjusted	No hysterectomy	1.00	0.35	1.00	0.05	1.00	0.001
Hysterectomy at age (yrs):	<40	1.75 (0.95, 3.23)		2.03 (1.21, 3.42)		2.18 (1.34, 3.54)	
	40-49	0.92 (0.53, 1.59)		1.12 (0.73, 1.72)		1.37 (0.94, 2.00)	
	≥ 50	0.96 (0.36, 2.57)		0.69 (0.28, 1.72)		1.59 (0.81, 3.12)	
HRT use at age 53 years (N=1465)							
Unadjusted	No hysterectomy	1.00	0.33	1.00	0.03	1.00	0.01
Hysterectomy at age (yrs):	<40	1.74 (0.98, 3.08)		2.14 (1.32, 3.45)		2.11 (1.33, 3.35)	
	40-49	0.96 (0.58, 1.58)		1.14 (0.77, 1.70)		1.30 (0.91, 1.88)	
	≥ 50	0.95 (0.37, 2.46)		0.87 (0.38, 1.97)		1.70 (0.89, 3.24)	
Adjusted	No hysterectomy	1.00	0.49	1.00	0.06	1.00	0.07
Hysterectomy at age (yrs):	<40	1.50 (0.84, 2.69)		1.98 (1.21, 3.23)		1.85 (1.16, 2.96)	
	40-49	0.86 (0.52, 1.45)		1.10 (0.73, 1.65)		1.15 (0.79, 1.67)	
	≥ 50	0.88 (0.34, 2.28)		0.85 (0.37, 1.94)		1.47 (0.76, 2.82)	

* No hysterectomy or oophorectomy

Chapter 11: Hysterectomy, psychological health and perceptions of the effect of the procedure on quality of life and wellbeing

Main objective: To investigate whether hysterectomy is associated with subsequent psychological health and to examine whether psychological health and other factors affect women's perceptions of the effect of their hysterectomies on quality of life and wellbeing.

11.1 Introduction

In 2001, poor psychological health, specifically unipolar depressive disorder, was one of the ten leading causes of burden of disease in low-, middle- and high-income countries.[468] In the UK approximately 40% of people who receive incapacity benefits do so because of mental illness and approximately one third of a general practitioner's time is spent dealing with people reporting psychological problems.[469] It is thus important to try and identify factors which influence risk of this outcome, especially those which are modifiable or avoidable. Further, women have higher rates of many psychological disorders than men from late adolescence onwards[470-472] and so there is a need to try and identify risk factors specific to women which could explain this sex difference, one such potential factor is hysterectomy.

In addition to examining the association between hysterectomy and subsequent psychological health this chapter also examines women's perceptions of the effects of their hysterectomies on their quality of life and wellbeing. The psychological and somatic health experiences of women in the time period after their hysterectomy compared to their experiences prior to surgery are likely to influence their perceptions of the effect of the procedure on their quality of life and wellbeing and determine whether these perceptions are positive or negative. Assessing women's own perceptions of the overall effect of their hysterectomies and their satisfaction with the procedure is important. As Khastgir and Studd[56] reported in 2000, 'For a procedure such as hysterectomy, which aims to improve symptoms, the patient's satisfaction provides a more accurate reflection of outcome and should be the ultimate judge of success.'[56] (p.1431)

While women's perceptions of the effects of their hysterectomies are subjective they may provide a good indication of whether hysterectomy tends to cause overall improvements or deteriorations in health and quality of life. As well as women's psychological health potentially affecting their subsequent perceptions of hysterectomy it is also possible that women's experiences of hysterectomy may affect their subsequent psychological health, especially if their experience is negative or very positive.

11.2 Literature review

11.2.1 The association between hysterectomy and subsequent psychological health

As discussed briefly in chapter 8, section 8.2.3.9, the belief that hysterectomy impacts detrimentally on subsequent psychological health was widely held throughout the majority of the twentieth century.[46] There have been a number of comprehensive reviews of the literature on this association published since 2000[406;410;473] and these all report that results from empirical studies are conflicting - while many earlier studies found evidence to support the notion that hysterectomy is detrimental to psychological health[474-476] other studies have not found an association or have found that hysterectomy is associated with improvements in psychological health.[8;46;310;406;410;413;473;477-483] The inconsistencies between studies are due in part to the range of different methodologies, measures of psychological health and study populations which have been employed to test the association. The studies which have found a detrimental effect of hysterectomy have tended to be retrospective. Prospective studies which have included measures of pre-hysterectomy psychological health suggest that a negative effect of hysterectomy on psychological outcomes may have been found not because of a direct effect of hysterectomy on subsequent psychiatric outcomes but because women who undergo hysterectomy have poorer psychological health prior to surgery than other women. When prior psychological status has been taken into account, studies have tended to find that there is no effect of hysterectomy on subsequent psychological health or that there are improvements in psychological health post-procedure.[406;413;477;480]

Studies which take into account prior psychological health address a major limitation of many earlier studies. However, these studies often have other limitations including a lack of non-hysterectomised comparison groups, with measures of psychological health pre-hysterectomy simply compared to measures post-hysterectomy.[477;480] This is a major limitation given changes in psychological health occur with age regardless of hysterectomy status. A further limitation is small sample size (for example, in one study there were only 9 hysterectomised women).[413] Short length of follow-up (often of less than 2 years)[413;477;480;481;483;484] is also a limitation of most existing studies especially if the impact of hysterectomy on psychological health across the remainder of life is to be assessed - an effect of hysterectomy may take time to manifest or conversely be transient and so only seen while women are in the recovery period after surgery and this needs to be assessed. Everson and colleagues[413] have noted a further limitation which is that studies which include pre-hysterectomy measures of psychological status often measure this very close to the time of the procedure (i.e. less than four weeks before hysterectomy).[477;480;481;483] At this time levels of symptoms of poor psychological health such as anxiety and depression may be greatly elevated due to concerns about the impending major surgery the women are to undergo. These measures may therefore not be an accurate reflection of prior psychological status whereby adjustment for them could be an over-adjustment and lead to the attenuation of what is a real detrimental effect of hysterectomy. These limitations can be avoided using data from the NSHD.

In examining the relationship between hysterectomy and psychological health it is important to consider factors that may modify it. A range of factors have been proposed by authors[413;473-475;480;485] including age at time of the procedure, parity, marital status, SEP, reason for and route of hysterectomy and oophorectomy status. Some studies have found that women who have a hysterectomy at a young age have higher risk of subsequent psychological problems than women who have hysterectomy at later ages, [413;475] but this is not consistent across all studies.[485] No variation in association by parity, oophorectomy status, route of procedure or SEP has been found.[474;480;485] Likewise no differences in effect by reason for hysterectomy has been found in some studies,[480] although in others an absence of an underlying pathology was associated with increased risk of poor psychological outcome.[474] As well as prior poor psychological status placing women at increased risk of poor psychological health post-hysterectomy, measures of prior psychological vulnerability as indicated by marital disruption and neuroticism also increased the likelihood of women experiencing psychological problems post-procedure.[474;480;484] It seems necessary to investigate these factors further as variation in outcome by such factors may provide clues as to the underlying pathways between hysterectomy and psychological health. For example, it seems important to consider variation by reason not only because women with no underlying pathology may have potentially different outcomes, related to the fact that women with pre-existing psychological problems may be more likely to report gynaecological symptoms in the absence of an underlying pathology, but because the effect on psychological health of a hysterectomy performed for cancer may be very different from the effect of a hysterectomy performed for a benign disorder. Variation by age at hysterectomy is also potentially important; for example, the loss of fertility which is considered by many to be an important consequence of hysterectomy and which is thought to impact on psychological health may have differing effects on psychological health dependent on the age it was lost and the length of expected reproductive life lost.

Why women with poorer psychological health are more likely to undergo hysterectomy is likely to be explained by the widely reported association between gynaecological and psychological symptoms.[486-488] Women who have higher levels of depression, anxiety and neuroticism have been found to be more likely to report higher levels of gynaecological symptoms such as abnormal bleeding than other women[486-488] and therefore these women are more likely to have contact with a gynaecologist and thus be referred for a hysterectomy. Associations are seen between a range of somatic symptoms and psychological health[489;490] with the suggestion that people with psychiatric disorder report physical symptoms as a means of seeking medical attention while denying their psychological problems, a process known as 'somatisation'.[491] However, while it is possible that the psychological problems are primary and lead to an amplification or misinterpretation of gynaecological symptoms which in women with good psychological health might have been ignored it is also possible that in some women, the gynaecological symptoms are primary and the experience of these causes subsequent distress and other psychological problems, especially amongst vulnerable women.[487;492] In a study of the temporal association between a range of physical symptoms and psychological health in the NSHD, it was found that the association between the reporting of psychological and physical symptoms operates in both directions.[492]

In addition to women with poor psychological health having a greater risk of hysterectomy, there are other reasons why hysterectomy may be associated with subsequent psychological health. As described in chapter 8, section 8.2.3.5, hysterectomy may cause changes in hormone exposure even with ovarian conservation and these could affect psychological health. Further, hysterectomy may cause scarring, loss of feminine self image, strength and self esteem and feelings of distress at the loss of fertility[473] all of which could lead to poor psychological health. Further, hysterectomy may be perceived as a stressful life event for some women and so could provide the necessary trigger, especially amongst those who are vulnerable, to increase women's psychological distress to the point where it becomes a clinically recognised condition.[473] Conversely, hysterectomy could have a positive effect on subsequent psychological health by reducing anxiety about gynaecological problems and by providing relief from gynaecological symptoms which had previously been detrimentally affecting quality of life and psychological health.

11.2.2 Women's own perceptions of the effect of their hysterectomies

A number of studies have examined women's own perceptions of the effect of their hysterectomies.[55-57;228;229;317-319;493] These have all found that the majority of women report satisfaction with the procedure and improvements in quality of life following surgery. These positive experiences are thought to be due at least in part to the relief of gynaecological symptoms which women were experiencing prior to surgery. In one study[229] high patient satisfaction was found despite the fact that a significant proportion of women in the study perceived that a range of symptoms had been made worse or caused by hysterectomy. This suggests that in assessing the effect of their hysterectomies women compare their pre- and post-hysterectomy health and can consider the procedure to be of benefit even if they believe new symptoms have developed as a result of the procedure. This highlights the point made by Ferroni and Deeble[55] that even if a woman reports a positive overall experience this does not imply that all outcomes experienced were favourable, only that they were better than the woman's past experiences.

The findings of positive perceptions of hysterectomy and high levels of satisfaction are very encouraging findings for doctors and surgeons and reassuring for women due to undergo the procedure. However, there are women in each study who reported negative experiences of and dissatisfaction with the procedure, who did not benefit from the relief of existing symptoms and developed new ones. Given the majority of hysterectomies are elective and are performed to improve quality of life it would be hoped that the number of women dissatisfied with the procedure should be minimal. Improvements to the service women receive may help reduce this number further. Identifying the factors which influence whether women experience a positive or negative experience of hysterectomy is thus important as this information would enable the development of a profile of women who are at greatest risk of suffering from negative self-perceived experiences of hysterectomy and who may therefore require further counseling prior to undergoing any procedure and greater levels of support post-procedure. Only a few studies have attempted to identify such factors and from these it is not possible to establish one clear set of factors that are important. In a study of women enrolled in the Maryland Women's Health study, Kjerulff and colleagues found that dissatisfaction with the procedure was associated with lower levels of education, depression, readmission to hospital and a lack of symptom relief[317] and that lack of symptom relief was associated with being in therapy for emotional or psychological problems, depression, low household income and concomitant bilateral oophorectomy.[319] In other studies dissatisfaction has been found to be associated with: a negative outlook toward hysterectomy prior to surgery; slower post-operative recovery; a lack of symptom relief; depression; reductions in sexual activity;[56] lower income;[493] high parity; later age at hysterectomy; and prior symptoms perceived to be less severe.[229] Where more than one study has examined the same factor the findings were not always consistent – while other investigators found that age and concomitant oophorectomy were associated with satisfaction or symptom relief, Unger and colleagues[493] found no variation in satisfaction by these factors or by race or reason for or route of hysterectomy. This existing research suggests that women's health, particularly their psychological health, socioeconomic factors, reproductive characteristics and characteristics of hysterectomy, could all be associated with women's own perceptions of the effects of their hysterectomy and so require further investigation.

11.2.3 Selecting appropriate covariates

To assess the effect of hysterectomy on subsequent psychological health it was necessary, as in the previous two chapters, to identify factors from across life which could predict both psychological health in middle-age and hysterectomy risk and which could therefore act as confounders of the association. The selection of covariates was informed as follows.

Research suggests that women who suffer from psychological problems in middle-age have followed different life course trajectories to women not suffering from such problems[419] confirming the need to take a life course perspective when selecting appropriate covariates. As the association between hysterectomy and subsequent psychological health could be explained by prior psychological status this is the most important covariate to consider in analyses. Adjustment only for prior psychological status may not however, capture fully the different psychological experiences across earlier life that influence women's risk of suffering from poor psychological health in middle-age, especially as psychological health across adulthood in the NSHD is not stable.[494] It is thus important to also include markers of vulnerability to psychological problems. It has been shown that characteristics of vulnerability such as neuroticism predict higher levels of gynaecological symptom reporting[487] and so may predict hysterectomy risk. Markers of vulnerability in earlier life such as parental divorce, own and mother's neuroticism and anti-social behaviour and, in later life such as emotional support and social networks were also associated with psychological health in middle-age in the NSHD and so are potential covariates.[419;494;495]

Of the variables which have been found in this thesis to predict hysterectomy rates in the NSHD, a number have also been found to predict psychological health in adulthood. Providing a further demonstration of the number of adult health outcomes which are socioeconomically graded, not only has SEP across life been found to be associated with hysterectomy in the NSHD (shown in chapter 4), but low SEP at time points across life has also been found to be associated with higher levels of vulnerability and poor psychological outcomes in adulthood.[419;494;496;497]

Chapter 5 showed that BMI was associated with subsequent hysterectomy rates. Analyses have also found that BMI may be associated with psychological health in middle-age with women who were not of normal BMI at 43 years (i.e. underweight or overweight/obese) at higher risk of subsequent poor psychological health than women who had normal BMI in the NSHD.[419]

Although not investigated in this thesis there is some evidence from analyses in the NSHD (unpublished) that cognitive function in childhood was associated with hysterectomy risk in the NSHD independent of educational level, with women who had higher cognitive scores experiencing lower risk of hysterectomy. There is also evidence from the NSHD that women who had higher cognitive scores in childhood had lower i.e. better General Health Questionnaire (GHQ) -28 scores at age 53 years,[498] the measure of psychological health also used in this chapter, which suggests that cognitive function in childhood should be considered in analyses.

In the previous two chapters it has been necessary to include HRT use in analyses as this was associated with hysterectomy status in the NSHD[417] and has also been found to be associated with potentially lower risk of the outcomes under investigation. In this chapter there is a need to consider HRT use because as well as being associated with hysterectomy, HRT use was associated with increased risk of poor psychological health in the NSHD.[416;418] While smoking behaviour, which could be a risk factor for hysterectomy given the link between smoking and menstrual irregularity and oestradiol metabolism,[132] has not been investigated in this thesis, analyses (results not shown) suggest that ex-smokers may have reduced risk of hysterectomy compared to never smokers in the NSHD, possibly because of a 'healthy' ex-smoker effect. As smoking status and hysterectomy were associated in the NSHD and smoking behaviour was also found to be associated with psychological health in middle-age - women who were current smokers at age 43 years had increased risk of subsequent psychological distress[419] which has also been found in other studies[499] - it seems appropriate to consider it in these analyses.

11.3 Specific objectives of the chapter

The specific objectives to be addressed in this chapter are:

i. to examine whether hysterectomy is associated with subsequent psychological health

ii. to examine whether the association between hysterectomy and psychological health differs by oophorectomy status, reason for and route of operation, age at hysterectomy and menopausal status at time of hysterectomy
iii. to examine whether the association between hysterectomy and subsequent psychological health is independent of pre-hysterectomy psychological health and factors which predict psychological health in middle-age and hysterectomy risk
iv. to examine women's perception of the effect of their hysterectomy on their quality of life and wellbeing and to investigate factors which might influence this perceived effect

11.4 Methods

11.4.1 Methods used to address objectives (i) to (iii)

11.4.1.1 Main outcome variable

GHQ-28 score as a measure of psychological health at age 53 years

11.4.1.2 Main explanatory variable

Hysterectomy status

11.4.1.3 Covariates

Psychological health prior to hysterectomy, measures of vulnerability (parental divorce, mother's neuroticism, own neuroticism at age 16 years, anti-social behaviour at age 15 years, emotional support in adulthood and social networks in adulthood), lifetime SEP (father's occupational class in childhood, maternal education level, own occupational class in adulthood and educational level attained), BMI at age 26 years, cognitive function at age 8 years, history of HRT use at age 53 years and smoking behaviour at age 36 years

11.4.1.4 Exclusions

Women whose hysterectomy or oophorectomy was performed at or after age 53 years (given these analyses aimed to test the association between hysterectomy and *subsequent* psychological health).

11.4.1.5 Description and ascertainment of outcome variable

The outcome measure of psychological health used in these analyses was the GHQ-28 score. The GHQ-28 is a validated 28 item instrument (see appendix 10 for a summary of the 28 items) which has been designed to detect symptoms of anxiety and depression and psychosocial functioning[500;501] and is often used in studies as a measure of psychological distress.[502;503] This questionnaire was administered to the NSHD cohort members during the home visit at age 53 years. To obtain an overall score from the responses to the 28 items, each item was coded as absent or present using a 0-0-1-1 coding of the Likert responses. The scores from each item were then summed to create a total score ranging from 0 (best psychological health) to 28 (poorest psychological health). The distribution of GHQ-28 scores among women in the NSHD was right-skewed and there was a floor effect whereby approximately 45% of women reported an absence of all 28 items i.e. had a total score of 0. GHQ-28 score is usually found to be right-skewed in populations and to deal with this researchers often create a dichotomous variable. However there is variation between populations in the threshold score of GHQ-28 above which psychiatric morbidity is expected to be present[504;505] and it is possible that there is a continuum of increasing psychological morbidity across the entire scale.[471] To avoid selecting an inappropriate threshold by using an arbitrary cut-point and, to maximise power in analyses, a continuous GHQ-28 score was used in the main analyses. The natural logarithm ($\log_e$) of the GHQ-28 score was used to reduce the skewness of the distribution. Using $\log_e$(GHQ-28) scores in models meant that the regression coefficients multiplied by 100 could be interpreted as the percentage difference in GHQ-28 scores.[506]

11.4.1.6 Ascertainment of covariates

Two measures of pre-hysterectomy psychological health were considered in analyses. The first was a summary measure of psychiatric disorder experienced between ages 15 and 32 years which was a composite of all relevant information from records collected between these ages. The second was the Present State Examination (PSE)[507] total score. The PSE, which has been shown to be a reliable and valid instrument for psychiatric assessment,[508] was administered by nurses fully trained to use this instrument during the home visit at age 36 years as a measure of the presence and severity of anxiety, depression and other psychological symptoms experienced in the month prior to the visit. Both measures, because they were highly right skewed, were categorised into three groups. The measure of prior psychiatric disorder between ages 15 and 32 years was grouped into: no psychiatric disorder (55.5%); minor or trivial nervous disorder (34.3%); severe disorder (which included: experience of psychiatric disorder for more than a year; four or more psychiatric episodes over more than a year; any out- or in-patient episodes of psychiatric disorder) (10.2%) and, the PSE score was grouped into: no symptoms (39.7%); 1-3 symptoms (31.5%); 4 or more symptoms (28.8%).

Of the measures of psychological vulnerability, parental divorce experienced by age 15 years was ascertained from information on parental marital status updated at data collections across childhood and was coded as a binary variable (yes vs. no). Mother's neuroticism was assessed by the mothers' completion of the Maudsley Personality Inventory when cohort members were aged 15 years. This was categorised into 7 groups on a scale from 0 (lowest level) to 6 (highest level of neuroticism). Cohort members' own levels of neuroticism were ascertained at age 16 years by completion of the neuroticism scale of the short Maudsley Personality Inventory.[509] Anti-social behaviour was ascertained from teachers' responses to a questionnaire they were asked to complete when the study participants were aged 15 years. This involved teachers rating study participants on 16 items describing personality, behaviour and attitudes based on comparison with other children in the same class. Both neuroticism and anti-social behaviour were categorised into 5 groups from lowest to highest levels of neuroticism and anti-social behaviour, respectively. Levels of emotional support and social networks in adulthood were ascertained from women's responses to a range of questions asked during the 1989 home visit. These questions asked about whether the cohort member lived with their partner, whether they felt they had emotional support and had people they could talk to and share feelings with and the frequency of social contact with friends and relatives. Both variables were categorised into 3 groups: poor; intermediate; good.

Details of the ascertainment of the four measures of SEP used in analyses were provided in chapter 4, of BMI at age 26 years in chapter 5 and of HRT use in chapter 9. Cognitive function at age 8 years was ascertained using four tests devised by the National Foundation for Educational Research[510] which assessed reading comprehension (sentence completion), pronunciation, vocabulary and non-verbal reasoning. Scores from these four tests which were taken at age 8 years were standardised and summed to generate a score of cognitive ability, this total score was then standardised for the sample included in this chapter's analyses. Smoking behaviour was recorded during the home visit at age 36 years when study participants were asked whether they had ever smoked cigarettes and, if they said no, whether they had ever smoked as much as one cigarette per day for as long as a year.[511]

BMI at age 26 years was included as a categorical variable given its non-linear association with both hysterectomy and psychological health and grouped into the 4 standard categories (<20; 20-25; 26-30; > 30 kg/m^2). Father's and own occupational class and maternal education were also grouped into 4 categories, educational level into 5 and HRT use into 3, all as described in chapter 9. Smoking status at age 36 years was categorised into 3 groups (lifelong non-smoker; current smoker; ex-smoker) and cognitive function was categorised into quartiles.

Statistical methods are presented after the description of the variables used in analyses to address objective (iv).

11.4.2 Methods used to address objective (iv)

11.4.2.1 Main outcome variable

Women's self-perceived effect of hysterectomy on quality of life and wellbeing

11.4.2.2 Explanatory variables

Characteristics of hysterectomy (oophorectomy status, reason for hysterectomy, route of hysterectomy, age at hysterectomy and menopausal status at time of hysterectomy), health status in middle-age (psychological health at age 53 years, functional limitations at age 53 years, physical performance at age 53 years, BMI at age 53 years, timing of onset of vasomotor symptoms), socioeconomic and reproductive factors (father's occupational class, maternal education level, own educational level, own and head of household occupational class in adulthood and parity at age 53 years) and cognitive function in childhood

11.4.2.3 Exclusions

All non-hysterectomised women and, hysterectomised women who had not responded to the 2005 questionnaire.

11.4.2.4 Description and ascertainment of outcome variable

Women's perceptions of the effect of their hysterectomies on quality of life and wellbeing were ascertained from response to the question 'How would you say that the operation to remove your uterus and/or ovaries affected your wellbeing and quality of life?' which was asked in the postal questionnaire sent in 2005 to women who had undergone a hysterectomy, as described in chapter 2, shown in appendix 1. The five response options to this question were: had a very good effect; had a good effect; had neither a good or bad effect; had a bad effect; had a very bad effect.

For the purposes of analysis self-perceived effect of hysterectomy was categorised into three groups: very good or good effect; neither good nor bad effect; bad or very bad effect.

11.4.2.5 Ascertainment of explanatory variables

Factors which it was thought could predict women's perceptions of the effect of their hysterectomy on quality of life and wellbeing were selected on the basis of previous research. This had suggested, as described in the literature review above, that characteristics of hysterectomy, health status in middle-age, socioeconomic factors and parity could affect women's perceptions. Factors from early life were also selected as it was thought that they too could influence women's perceptions of the effect of hysterectomy even though they had not previously been considered.

Details of the ascertainment of the five characteristics of hysterectomy were provided in chapter 2, of GHQ-28 (the measure of psychological health used in analyses) in the methods section above, functional limitations and physical performance at age 53 years in chapter 10, BMI at age 53 years in chapter 5, the indicators of SEP in chapter 4, parity in chapter 6 and cognitive function at age 8 years above. The timing of onset of vasomotor symptoms was ascertained from women's responses to the 'Women's Health in the Middle Years' postal questionnaires. In the first of these, sent in 1993, when the women were aged

47 years they were asked 'Have you ever experienced hot flushes?' and 'Have you ever experienced cold sweats or night sweats?' if the women answered yes to these questions they were then asked to provide the dates (month and year) or ages (in years) when these two symptoms were first experienced. In all subsequent annual questionnaires up to and including the questionnaire sent in 2000 women were asked to report whether they had experienced hot flushes and whether they had experienced cold or night sweats in the previous 12 months. If women reported an age at onset of hot flushes in the 1993 questionnaire they were assigned this age as their timing of onset of hot flushes. If they reported in 1993 that they had not experienced hot flushes but reported suffering from such symptoms in a subsequent questionnaire their age at onset of hot flushes was assigned as the age in years at the time when they first reported having suffered from hot flushes in the previous 12 months. This same method was used to assign a timing of onset of cold/night sweats. As hot flushes and cold/night sweats are both components of the same set of symptom experiences, as demonstrated by Kuh and colleagues using factor analysis,[416] information on the timing of these two symptoms was combined to create a variable of the timing of onset of vasomotor symptoms. Age at onset of vasomotor symptoms was taken as the age at onset of whichever of the two symptoms women reported having come first.

The characteristics of hysterectomy variables were categorised as described in chapter 8, section 8.4.4, except for reason for hysterectomy which was categorised as: benign vs. cancer. The GHQ-28 score was categorised into three groups based on expectations about thresholds above which psychological disorder would be present: 0-4; 5-13; 14-28. The three measures of functional limitation at age 53 years were categorised as described in chapter 10 and the three measures of physical performance were grouped into tertiles. BMI was categorised into 3 groups with normal and underweight women grouped together because of the small number of women who were underweight at age 53 years: ≤ 25 ; 25.1 – 30; > 30 kg/m^2. The timing of onset of vasomotor symptoms was categorised into 3 groups: ≤ 40; 41 – 45; ≥ 46 years. Father's occupational class, maternal education, own educational level and own and head of household occupational class in adulthood were categorised as described in chapter 5. Parity at age 53 years was categorised into 5 groups: 0; 1; 2; 3; ≥ 4 children and cognitive function at age 8 years was categorised into quartiles.

11.4.3 Analyses

11.4.3.1 Analyses to address objective (i) – unadjusted association

A comparison of mean values of the $\log_e$(GHQ-28) score at age 53 years by prior hysterectomy status was performed using one-way analysis of variance and a linear regression model.

11.4.3.2 Analyses to address objective (ii) – characteristics of hysterectomy

The above analysis was rerun with prior hysterectomy status categorised by each of the characteristics of hysterectomy described in chapter 8.

Using likelihood ratio tests, linear regression models of the association between each characteristic of hysterectomy and $\log_e$(GHQ-28) score were compared to a linear regression model in which all hysterectomies were grouped together. Women who had undergone an oophorectomy only were excluded from all analyses except those assessing the difference in associations by oophorectomy status.

11.4.3.3 Analyses to address objective (iii) – adjusted associations

Before performing any adjusted analyses checks were performed to ensure that all covariates selected by literature review met the definition of a potential confounder/effect modifier i.e. were associated with the main explanatory variable and with the outcome. Covariates were included in adjusted models if tests of association with both the outcome and explanatory variable produced p-values of 0.10 or less. It was especially important to perform these tests for the markers of vulnerability in earlier life and adulthood as the associations between these variables and hysterectomy risk had not previously been tested in the NSHD or other studies.

Using multiple linear regression models the association between hysterectomy status and $\log_e$(GHQ-28) score at age 53 years was adjusted in separate models for each of the following sets of covariates which were found to meet the definition of a potential confounder: psychiatric state between ages 15 to 32 years; PSE score at age 36 years; markers of vulnerability in childhood and adulthood (parental divorce, mother's neuroticism, own neuroticism at age 16 years, anti-social behaviour at age 15 years, emotional support in adulthood and social networks in adulthood); lifetime SEP (father's occupational class in childhood, maternal education, educational level and own occupational class in adulthood); BMI at age 26 years; cognitive function at age 8 years; smoking status at age 36 years; and history of HRT use. Those covariates listed which did not meet the definition of a potential confounder/effect modifier were not adjusted for in analyses.

As the PSE score at age 36 years was included as a measure of pre-hysterectomy psychological status, models including PSE score excluded not only women whose hysterectomy or oophorectomy occurred at or after age 53 years but also those performed at or before age 36 years, similar exclusions were not considered necessary when adjusting for prior psychiatric state between ages 15 to 32 years as this was a measure which captured prior psychological health even for those women who had an early age at hysterectomy. Likelihood ratio tests were performed to test for interaction between both measures of prior psychological health, measures of vulnerability and hysterectomy status given the suggestion, in the literature that, women who have prior psychological disorder and who are psychologically vulnerable may be at greater risk of poor psychological outcomes resulting from hysterectomy than other women.

In a final set of models including only those women with complete data on hysterectomy status and all other covariates identified as important, the association between hysterectomy status and $\log_e$(GHQ-28) scores at age 53 years was individually adjusted for each set of covariates. All covariates were then mutually adjusted for in a final model.

To maximise statistical power the above analyses were first run with hysterectomy status categorised as no hysterectomy or oophorectomy vs. hysterectomy with or without oophorectomy. The analyses were then rerun with hysterectomy categorised by any characteristic identified as significant in analyses to address objective (ii) and which it was thought could be explained by confounding. Women who had had an oophorectomy only were excluded from all these models as the regression coefficients estimated for the oophorectomy only group, as in analyses in the previous chapters, were unstable.

11.4.3.4 Analyses to address objective (iv) – predictors of perceived effect of hysterectomy

The associations between perceived effect of hysterectomy and each potential explanatory factor were tested using chi-squared tests. Polychotomous logistic regression, with very good or good perceived effect as the baseline outcome, was then used to produce estimates of the size of these associations. From unadjusted analyses those explanatory variables which were significantly associated with perceived effect were identified, these were then mutually adjusted for in multivariable polychotomous logistic regression models to identify those explanatory factors which were independent of others. Women who had missing data on any of the variables to be included in multivariable analyses were excluded to ensure that all models had the same N and were directly comparable.

11.5 Results

11.5.1 Results from analyses to address objective (i) - unadjusted association

There was no significant association between hysterectomy status and GHQ-28 score at age 53 years when grouping all hysterectomies together, table 11.1. Women who had previously undergone hysterectomy had GHQ-28 scores at age 53 years 9% higher than women who had not undergone a hysterectomy or oophorectomy but this was not significant at conventional levels.

11.5.2 Results from analyses to address objective (ii) - characteristics of hysterectomy

There was evidence of differences in the effect of hysterectomy by all characteristics except oophorectomy status, table 11.2.

Results from analyses by reason for hysterectomy suggest that women who had a hysterectomy for cancer had GHQ-28 scores at age 53 years which were 49% higher than women who had not had a hysterectomy or oophorectomy and that this difference was significant. No other reason for hysterectomy was significantly associated with elevated GHQ-28 scores at age 53 years.

There was also significant variation in the effect of hysterectomy by age at procedure - women who had undergone a hysterectomy before age 40 years had GHQ-28 scores at age

53 years 35% higher than women who had not had a hysterectomy or oophorectomy whereas women who had hysterectomies at a later age had very similar GHQ-28 scores to women who had not had a hysterectomy or oophorectomy.

Results from likelihood ratio tests suggested that there was a significant difference in effect by menopausal status at the time of the procedure - women who underwent pre-menopausal hysterectomies had higher GHQ-28 scores and women who underwent post-menopausal hysterectomies had lower GHQ-28 scores than women who had not undergone hysterectomy or oophorectomy. However, neither of these differences compared to the baseline were significant and this effect was found to be explained by the variation in the association between hysterectomy and GHQ-28 scores by age at procedure when both age and menopausal status were included in the same model (results not shown).

While there was no significant variation in GHQ-28 scores by route of procedure overall, women who had an unknown route of procedure had significantly higher GHQ-28 scores than women who had not undergone a hysterectomy or oophorectomy. This effect was thought to have been found because women with poor psychological health were more likely to have missing data and so this was not investigated further.

11.5.3 Results from analyses to address objective (iii) - adjusted associations

Own neuroticism and anti-social behaviour in adolescence, and emotional support and social networks in adulthood did not meet the criteria for inclusion in adjusted models as none of these factors were associated with hysterectomy. Experience of parental divorce and maternal neuroticism did meet the criteria for inclusion with women who had experienced parental divorce by age 15 years and women whose mothers were more neurotic having higher risk of hysterectomy at younger ages.

In models in which all hysterectomies were grouped together none of the adjustments made altered the point estimates of effect greatly and there remained in all models no significant association between hysterectomy and GHQ-28 scores. In tests of interaction, there was no evidence that prior psychological status or vulnerability modified the effect of the association between hysterectomy and subsequent psychological health (results not shown).

The association between age at hysterectomy and GHQ-28 scores could be explained by confounding so this association was also examined using multivariable analyses. As done in the adjusted analyses in the previous chapter age at hysterectomy was grouped into four categories (no hysterectomy or oophorectomy; hysterectomy at < 40; 40-49 years; ≥50 years) instead of five as prior analyses suggested no difference between groups aged 40-44 and 45-49 years. In addition women whose hysterectomy was for cancer were excluded in order that the effect of age at hysterectomy on GHQ-28 scores could be examined independently of the detrimental effect on psychological health of having a hysterectomy for cancer. PSE scores were not considered in models of the association between age at hysterectomy and GHQ-28 scores as when PSE scores were included women who had a hysterectomy before age 36 years had to be excluded and this meant excluding many of the women in the group of most interest.

After exclusion of women who had hysterectomy for cancer, there remained a significant unadjusted association between age at hysterectomy and GHQ-28 scores suggesting that the effect of age at hysterectomy was independent of the effect of cancer. Of all the covariates adjusted for in analyses the only two which altered the estimate of effect of young age at hysterectomy on GHQ-28 score at age 53 years were prior psychiatric state and HRT use, table 11.3. Adjustment for these variables caused the regression coefficients of the effect of young age at hysterectomy to attenuate. However, confounding by these variables was only partial as women who had a young age at hysterectomy (i.e. less than 40 years) still had GHQ-28 scores over 30% higher than women who had not had a hysterectomy or oophorectomy after adjustment. Psychological vulnerability (as indicated by maternal neuroticism and parental divorce), lifetime SEP, cognition at age 8 years, BMI at age 26 years and smoking status did not appear to confound the association between age at hysterectomy and GHQ-28 scores. In tests of interaction, there was no evidence that prior psychological status or vulnerability modified the effect of the association between age at hysterectomy and subsequent psychological health (results not shown).

When prior psychological state and HRT use were adjusted for in the same model (results not shown) the effect of young age at hysterectomy on GHQ-28 scores retained statistical significance at conventional levels. Adjustment for additional variables had no effect.

11.5.4 Results from analyses to address objective (iv) - predictors of perceived effect of hysterectomy

Of the 316 women who had undergone a hysterectomy in the NSHD and provided a response to the question asked about the effect of their hysterectomy on their subsequent quality of life and wellbeing, 265 (83.9%) reported that their hysterectomy had a very good or good effect. Only 14 (4.4%) women reported that their hysterectomy had a very bad or bad effect and the remaining 37 (11.7%) reported that it had neither a good nor bad effect.

In unadjusted analyses factors associated with self-perceived effect of hysterectomy on subsequent quality of life and wellbeing were: concomitant oophorectomy; reason for hysterectomy; timing of onset of vasomotor symptoms; and psychological health at age 53 years, table 11.4. Women who had undergone a concomitant oophorectomy were over 3 times more likely to perceive that their hysterectomy had a bad or very bad effect compared to women who had undergone a hysterectomy but not an oophorectomy. Women who had undergone hysterectomy for cancer were nearly 7 times more likely to perceive that their hysterectomy had neither a bad nor good effect compared to women who had undergone a hysterectomy for a benign reason but these women were not significantly more likely to perceive that their hysterectomy had a bad or very bad effect. Women who had experienced the onset of vasomotor symptoms at or before age 40 years were over 5.5 times more likely to report that their hysterectomy had neither a good nor bad effect and over 7 times more likely to report that it had a bad or very bad effect compared to women who experienced the onset of vasomotor symptoms at or after age 46 years. Women who were psychologically distressed i.e. had GHQ-28 scores at age 53 years greater than 13 were 8.5 times more likely to report that their hysterectomy had a bad or very bad effect compared to women who had a GHQ-28 score less than 5. Perceived effect of hysterectomy was not significantly associated with other characteristics of hysterectomy, measures of musculoskeletal health or BMI at age 53 years, any indicator of SEP, parity or cognition (see appendices 11 to 13).

In analyses in which all four variables found to be associated with self-perceived effect of hysterectomy were adjusted for each other most associations attenuated, table 11.5.

However, hysterectomy for cancer and experiencing onset of vasomotor symptoms at or before age 40 years remained significant predictors of perceiving that hysterectomy had neither a good nor bad effect, and GHQ-28 score of over 13 remained a significant predictor of perceiving that hysterectomy had a bad or very bad effect. Other associations were of borderline significance.

11.6 Discussion

11.6.1 Main findings

While there was no association between hysterectomy and subsequent psychological health at age 53 years overall, women in the NSHD who underwent a hysterectomy before age 40 years had significantly poorer psychological health at age 53 years than women who had not undergone a hysterectomy or oophorectomy or who had undergone a hysterectomy or oophorectomy at a later age. This association remained significant after adjustment for potential confounders such as prior psychological state, psychological vulnerability and lifetime SEP. Women who had previously undergone a hysterectomy for cancer also had significantly poorer psychological health at age 53 years than other women. These two effects were independent of each other.

Most women in the NSHD who had undergone a hysterectomy perceived that this had had a very good or good effect on their subsequent quality of life and wellbeing. Factors which predicted perceptions that hysterectomy had an indifferent or a bad or very bad effect were having a hysterectomy for cancer, concomitant oophorectomy, younger age at onset of vasomotor symptoms and poor psychological health.

11.6.2 Comparison with other studies

While many studies have examined the association between hysterectomy and subsequent psychological health previously, few are directly comparable to this study as the majority had a much shorter length of follow-up, have not considered variation in outcome by so many different characteristics of hysterectomy and have not assessed the role of confounders operating at different stages of life. Given the great amount of inconsistency between studies, results from different studies can be found which support or conflict with the findings from this study in approximately equal measure. While there was no overall association between hysterectomy and psychological health in the NSHD, which supports the findings from most recent studies,[406;473] this was masking an effect specific to young age at hysterectomy. The elevated risk of poor psychological health among women with young age at hysterectomy has been found in some other studies[475] but not others,[485] with no study with a fully satisfactory design having assessed this previously. The elevated risk of poor psychological health among women who had undergone hysterectomy for cancer found in this study suggests that other researchers were correct to exclude this group of women from their analyses. That there appeared to be no variation in association between hysterectomy and psychological health by oophorectomy status is supported by findings from other studies which have also found no detrimental effect of prophylactic oophorectomy on psychological outcomes.[512]

In previous analyses using data from the NSHD,[416] it was found that women who had previously undergone a hysterectomy had poorer psychological health at age 47 years than other women with the exception of HRT users. However, at slightly later ages no association between hysterectomy compared to other menopausal states and psychological symptom reporting was found.[418;419] This is consistent with the findings from these new analyses – an effect of hysterectomy on psychological health was probably found at age 47 years because of the effect of young age at hysterectomy on poor psychological health but in later analyses this effect will have been diluted by the inclusion of women whose hysterectomies occurred later and for whom there was no elevated risk of poor psychological health.

No study has conducted research which is directly comparable to this chapter's study of the perceptions of the effect of hysterectomy on quality of life and wellbeing and factors which predict this. That most hysterectomised women in the NSHD perceived a good or very good effect is consistent with the high levels of satisfaction with the procedure found in other studies.[55-57;229;317-319;493]

11.6.3 Explanation of findings

11.6.3.1 The association between hysterectomy for cancer and psychological health

The association between hysterectomy for cancer and higher GHQ-28 scores at age 53 years is most likely explained by the fact that being diagnosed and treated for cancer is detrimental to psychological health. There is consistent evidence to show that cancer, its treatment and its association with an uncertain future are associated with depression and anxiety and that psychological problems can persist even after the disease is successfully treated.[410;513]

Women who undergo hysterectomy for cancer are more likely to have a greater amount of tissue removed during surgery than women undergoing hysterectomy for other reasons. As their surgery is inevitably more radical, they are perhaps more likely to perceive that they have suffered greater alterations to their bodies, image and sense of femininity than other women who have undergone hysterectomy for benign reasons and so be more likely to suffer from elevated anxiety, distress and depression. However, this second explanation is likely to be minor compared to the much greater global effect which diagnosis for cancer independent of hysterectomy has on psychological health. This is especially true given it does not appear that the influence of changes to the body are greatly important to women in the NSHD - there was no significant variation in the effect of hysterectomy on psychological health and no significant difference in the risk of negative self-perceptions of the effect of hysterectomy by route of procedure even though abdominal hysterectomy would be expected to cause greater alterations to the body and self image than vaginal hysterectomy.

11.6.3.2 The association between age at hysterectomy and psychological health

A striking finding of these analyses was the greater risk of poor psychological health at age 53 years among women who underwent a hysterectomy before age 40 years and the partial independence of this association from prior psychological status, vulnerability and other potential confounders. This association between young age at hysterectomy and poorer health in middle-age was also found in the previous chapter and many of the potential explanations are similar.

In the previous chapter, one of the most likely explanations of the association between young age at hysterectomy and higher risk of poor musculoskeletal health was that women who had hysterectomies at younger ages had higher levels of risk factors for these outcomes than other women. Women in the NSHD who had hysterectomy at a young age had poorer psychological health prior to hysterectomy, lower SEP and higher levels of psychological vulnerability than other women. Therefore, it may have been expected that the association between young age at hysterectomy and increased risk of subsequent poor psychological health would be explained by the higher risk of poor psychological health which these women had compared to other women. However, as described above adjustment for these and other potentially confounding factors did not fully explain the association. It is possible that not all appropriate confounders were identified and that the association is explained by residual confounding. However, the problem of residual confounding should have been minimised as adjustments were made not only for prior psychological state but also indicators of psychological vulnerability and factors which strongly predict psychological health such as lifetime SEP. It is thus necessary to explore alternative explanations given the higher risk profile for poor psychological health which those women who had young age at hysterectomy had does not appear to fully explain the association.

The association between young age at hysterectomy and poor psychological health could be explained by a time lag effect. It is possible that it takes time for the detrimental effect of hysterectomy on psychological health to develop and it is only those women whose hysterectomy was performed before age 40 years for whom sufficient time has passed for the association to be seen at age 53 years and that a similar effect will also be seen in other hysterectomised women in subsequent years. However, this seems unlikely, especially as the effect of young age at hysterectomy on psychological health was already detectable by age 47 years[416] and there is no obvious pathway on which an effect of hysterectomy would take such a long time to manifest.

Another possibility is that there is something particularly harmful to psychological health about having a hysterectomy at a young age. The implication of this would be that if the women whose hysterectomies were performed before age 40 years had had their procedures delayed to a later age their psychological health at age 53 years would have been no different to other women's, a finding of potential clinical importance. One way in which hysterectomy could be more damaging the earlier it is performed is through its effect on hormone exposure. If hysterectomy is associated with reductions in oestrogen exposure, women exposed to these reductions at younger ages and further from the time that these would have naturally occurred (i.e. with menopause) may be at higher risk of conditions influenced by such reductions. Psychological health is influenced to some extent by hormone exposure[473] but there is little evidence that psychological health is affected directly by the hormonal changes usually associated with menopause.[418] Further, there was no significant variation in psychological outcome by oophorectomy status. This suggests that a pathway acting directly from hysterectomy through oestrogen exposure to psychological outcomes is unlikely to be operating. However, it is possible that the changes in hormone exposure which women experience if they undergo an oophorectomy and, may experience as a result of hysterectomy even if not accompanied by oophorectomy, could cause the onset of vasomotor symptoms and other symptoms associated with the menopause. The timing of the onset of these symptoms could affect psychological health. Onset of symptoms usually associated with the menopausal transition,[418] at an age earlier than is considered normal could cause anxiety and distress and impact on psychological health in ways not experienced by women whose symptoms occur closer to the age expected with natural menopause. Early onset of vasomotor symptoms was associated with higher GHQ-28 scores (results not shown) and with greater risk of negative self-perceptions of the effect of hysterectomy, table 11.4, suggesting that these symptoms were important to women and influence their perceptions and psychological health. However, as discussed in chapter 8, section 8.2.3.5, while there is some evidence that women who undergo hysterectomy without oophorectomy do experience earlier onset of vasomotor symptoms this has still not been conclusively shown. There is still a need to try and separate out whether there is an effect of hysterectomy independent of an effect of oophorectomy on such outcomes.

Feelings of regret and distress at the loss of fertility are often cited as a potential explanation of the association between hysterectomy and subsequent psychological health. It is possible that women who had hysterectomies at young ages were less able to have the number of children they desired because they lost more of their potential reproductive life than other women. This could result in women who had hysterectomies at younger ages suffering from greater feelings of loss and regret whereby they are more likely to develop poorer psychological health than other women. Although this explanation is plausible, those women in the NSHD who had hysterectomies at younger ages were no more likely to be nulliparous or have only one child than women who had hysterectomies at later ages. A test of interaction between age at hysterectomy and parity in a model of the association between age at hysterectomy and GHQ-28 scores found no evidence of effect modification and there was no association between parity and self-perceived effect of hysterectomy, suggesting that this explanation is not likely to explain the association found in the NSHD, unless women who had younger ages at hysterectomies had larger desired family sizes than other women which cannot be tested.

A further possibility is that women who had hysterectomies at a young age had hysterectomies for different reasons to those performed later. Gynaecological conditions resulting in hysterectomy at young ages may share a common aetiology with poor psychological outcomes or the conditions associated with hysterectomy at later ages may share a common aetiology with favourable psychological outcomes. An alternative to an aetiological link is that the conditions such as menstrual disorders associated with hysterectomy at young ages, may be less easily justified than other reasons when women come to reassess their decision to have undergone hysterectomy. If this was the case women who underwent hysterectomy at young ages may feel a greater sense of regret at having had the operation than women who had the operation at later ages and this level of regret could have impacted on subsequent psychological health. However, as shown in chapter 2 there was insufficient variation in reason for hysterectomy by age at operation for this to have driven the association between age at hysterectomy and psychological health found and as shown in table 11.2 there was no significant variation in the association between hysterectomy and subsequent psychological health by different benign reasons. Further, there was no variation in the self-perceived effects of hysterectomy by the different categories of benign reason as would have been expected if different conditions when reassessed by the women caused varying levels of feelings of regret at having undergone the operation.

If as proposed in chapter 10, hysterectomy at a young age is an indicator of the premature onset of chronic health problems usually associated with old-age this could explain the association between young age at hysterectomy and poor psychological health. The psychological health of women who experienced symptoms and health outcomes usually associated with ageing prematurely would be expected to be detrimentally affected. Whether hysterectomy at an early age is an indicator of the premature onset of chronic conditions associated with ageing which could explain the associations found between young age at hysterectomy and poor health in middle-age in the NSHD requires further investigation.

A period rather than an age effect could also be responsible for the association between young age at hysterectomy and poor psychological health found in the NSHD. Research by Gath and colleagues[514] has shown that among groups of women undergoing hysterectomy in Oxford, both pre- and post-hysterectomy levels of psychiatric morbidity fell significantly between 1975 and 1990. One proposed explanation of this decline was that clinicians changed their referral practices and whereas in 1975 doctors may have preferentially referred women who had psychological and gynaecological symptoms for hysterectomy, over time they may have become less inclined to refer women with psychological problems for hysterectomy. This proposed change in practice over time, whereby women with poor psychological health changed from being more likely to less likely to be referred to a gynaecologist is unlikely to fully explain the association found in the NSHD as such an effect will have been controlled for in analyses by adjusting for pre-hysterectomy psychological status. This study does however suggest that there have been relevant changes in medical practice over time. It is possible that with a growing recognition and concern among the medical profession that hysterectomy is associated with poor psychological health that in more recent years women of all ages have received greater amounts of counseling pre- and post-hysterectomy. In addition improvements in levels of patient autonomy could have resulted in women in more recent years having greater involvement in decision making processes whereby they subsequently suffer less from feelings of regret and loss of control at having undergone hysterectomy. If such changes have occurred then women in the NSHD who had a young age at hysterectomy will have had their hysterectomies at a time when there was less counseling and less opportunity for involvement in decision making processes which may have left them more vulnerable to psychological problems as a consequence of hysterectomy than women who had hysterectomies more recently i.e. at later ages. To examine whether there is an age or a period effect it would be necessary to examine the long-term association between hysterectomy and subsequent psychological health by age at hysterectomy in cohorts of women born in different years.

11.6.3.3 Factors which predict the self-perceived effect of hysterectomy on subsequent quality of life and wellbeing

A very high proportion of the hysterectomised women in the NSHD who returned the 2005 postal questionnaire reported that their hysterectomy had a positive effect on their quality of life and wellbeing. While it is possible that this is a real effect and represents the true level of positive self-perceptions of the effect of hysterectomy in the population, it is also possible that the women who responded to the 2005 questionnaire were not representative of all hysterectomised women in the NSHD and that this result is the consequence of bias. Comparison of the characteristics of the 316 hysterectomised women who responded to the appropriate question in 2005 and the 87 hysterectomised women who did not, either because they chose not to return the questionnaire or because they were not sent the questionnaire due to death, loss to follow-up or prior refusal to participate, found that there were no significant differences by any characteristic examined except reason for hysterectomy - women who had not answered the appropriate question in 2005 were significantly more likely to have had a hysterectomy for cancer than women who had answered the question (results not shown). While there were also small differences in educational level attained, BMI at age 53 years and psychological status at age 36 and 53 years between the two groups these were not significant. This suggests that the women who responded to the appropriate question were representative of all women who had a hysterectomy in the NSHD with the only significant difference resulting from the fact that women who had a hysterectomy for cancer were more likely to have died and so not have been sent the relevant questionnaire. Further, even if all the women who did not respond, had reported that their hysterectomy had a negative effect on their quality of life and wellbeing, which seems unlikely especially as women who have bad experiences are usually more likely to respond when asked for their opinions, the majority of women would still have been found to have reported that their hysterectomy had a positive effect.

The women's responses to the question in the 2005 questionnaire which asked 'What were the main ways in which the operation to remove your uterus and/or ovaries affected your wellbeing and quality of life?' provide some anecdotal evidence to explain why so many women perceived that their hysterectomy had a positive effect on their quality of life and wellbeing. The majority of responses to this question suggest that the gynaecological symptoms that women were experiencing prior to hysterectomy were detrimentally affecting their quality of life and wellbeing and that the relief from these symptoms following hysterectomy led them to believe that their hysterectomy had had a beneficial effect. These comments also suggest that the loss of menstruation was not considered to be detrimental by women in the NSHD even though this is often suggested by opponents of hysterectomy.[53] Comments made by women who reported a positive effect of their hysterectomy on quality of life and wellbeing:

'After the operation I was able to live a normal life'

'Made me less anxious and I felt more confident to go out and about'

'more energy, more able to cope with life'

'no more debilitating heavy periods and also the risk of pregnancy was ceased'

'I was free from almost continuous bleeding'

'No more periods'

'It was wonderful to be pain free and feel so much better. Every month I had at least 3 days when I could hardly hold myself up and spent at least one of these days lying down. Having the operation gave me a new lease of life. It was the best thing that ever happened to me.'

'I was able to enjoy life without having to arrange leisure time around painful periods.'

'No more excruciating pain each month, no more flooding and all that means'

'Having more energy and not feeling tired all the time'

'Freedom to lead a normal life without heavy bleeding and discomfort'

The women's comments also provided support for Ferroni and Deeble's[55] proposal that even if a woman reports a positive overall experience this does not imply that all outcomes they experienced were favourable, only that they were better than the woman's past experiences. A few of the women who reported that their hysterectomy had a positive effect overall also reported negative effects of their hysterectomy, the most common of which were loss of fertility and weight gain,

> *'I was no longer in pain....The only negative effect was I put on weight much more easily afterwards and obviously could not have more children, I was only 34, although I had 2 children and was happy with that, although they are 2 boys and may have been able to go on and have a girl'*
>
> *'No periods. Upset I could not have any more children'*

It is important to identify factors which predict negative or indifferent perceptions of the effect of hysterectomy on quality of life and wellbeing even though this applied to only a small proportion of women in the NSHD. The four factors (concomitant oophorectomy, reason for hysterectomy, timing of onset of vasomotor symptoms and psychological health) found to be significantly associated with self-perceived effect of hysterectomy on quality of life and wellbeing appeared to be acting at least partially independently of each other and so reasons for each association need to be considered separately. While other factors investigated were not found to be significantly associated with women's self-perceptions of the effect of hysterectomy this could be because they are not important factors or because there was insufficient power, given the small number of women who perceived a negative effect, to detect the levels of effect which existed.

Hysterectomy for cancer was most likely found to be associated with higher risk of perceiving neither a good nor bad effect of hysterectomy compared to having a hysterectomy for a benign reason because hysterectomy for cancer while acknowledged as a necessary and potentially life-saving treatment for gynaecological cancer is associated with a time in these women's lives during which they were diagnosed with a serious, potentially life-threatening condition, which is itself strongly associated with detrimental changes in quality of life and wellbeing.[410]

Poor psychological health could have been found to be associated with negative perceptions of the effect of hysterectomy for a number of reasons. Firstly it is possible that for those women who had experienced declines in psychological health since their hysterectomy they attributed these to the operation. Alternatively, it is possible that women who had poor psychological health were more likely to have negative opinions about all things they were asked about including the effect of their hysterectomy.

Age at onset of vasomotor symptoms and concomitant oophorectomy could both be associated with perceptions of the effect of hysterectomy on a similar pathway as both are associated with oestrogen exposure. Young age at onset of vasomotor symptoms was associated with risk of both negative and indifferent perceptions of the effect of hysterectomy. This is possibly because such symptoms are perceived by women to have been directly caused by hysterectomy. Suffering from such symptoms earlier than would be expected with natural menopause may be distressing and perhaps unexpected whereby it impacts more on quality of life and wellbeing than if experienced at a later age. Concomitant oophorectomy could be associated with higher risk of negative perceptions of the effect of hysterectomy because women who undergo this operation are more likely to experience early onset of vasomotor symptoms given the operation results in a guaranteed decline in oestrogen exposure with which the onset of vasomotor symptoms are associated. Alternatively it could be that women who have undergone prophylactic oophorectomy now consider that this was unnecessary and so feel greater levels of regret at having undergone the operation.

Responses to the question asked about the main ways in which hysterectomy affected quality of life and wellbeing of the women who reported a negative effect of hysterectomy, highlight the importance of the onset of vasomotor symptoms. Lack of pain relief, damage caused during the procedure, weight gain and the development of health outcomes which women have attributed to hysterectomy even though it may not have caused them (e.g. asthma) also seem to be important. Comments made by women who reported a negative effect of their hysterectomy on quality of life and wellbeing:

> *'Started menopause, had flushes, weight gain, mood swings, felt ill all the time'*
>
> *'Sleepless nights, night sweats, aching bones, hot flushes after I had the operation'*
>
> *'Abrupt menopause, hot flushes etc. accelerated osteoporosis'*
>
> *'Brought on early menopause, depression – felt unfeminine, lower back pain, prolapse bladder'*

'Went on HRT which made me dizzy and sick, came off and had to put up with irratibility (sic), hot flushes, night sweats. No sleep. Nerves have got much worse'

'The operation helped by treating the painful periods but approximately 6 months later I started having very strong menopausal symptoms.'

'Continue to endure lower left front pelvic pain when I exercise....Gained more than 2 stone weight when plunged into surgical menopause.....slight depression because unhappy with excess weight'

'Put on weight and felt tired all the time.....a few years ago I...found out that my lower intestine was damaged during the hyst'

'Discomfort around abdomen'

'General health declined – developed asthma, joint problems'

11.6.4 Limitations

While it was possible in analyses of the association between hysterectomy and psychological health to adjust for a pre-hysterectomy measure of psychological health, it was not possible to adjust for exactly the same measure i.e. GHQ-28 score as different measures of psychological health were used at different ages in the NSHD. Further, by adjusting for prior psychological health at only one age the true pre-hysterectomy psychological state of women may not have been appropriately captured especially given the variation in age at hysterectomy and hence time between the pre-hysterectomy measure of psychological health having been recorded and hysterectomy occurring. While, as discussed above, this as well as the potential failure to identify all important confounders could mean that there is residual confounding, the additional adjustment for factors from across life which strongly predict psychological health across adulthood would be expected to minimise this. In an ideal study the same measure of psychological health would have been measured repeatedly at regular intervals across time so that any changes in psychological health which occurred and the relation of these changes to the timing of hysterectomy could be examined more closely.

As in the previous two chapters, the analyses of psychological health excluded women who had hysterectomies or oophorectomies at or after age 53 years in order to establish a clear temporal relationship between hysterectomy and subsequent health. It is thus not possible to test whether hysterectomies performed at later ages had a different effect on subsequent psychological health to those performed before age 53 years. However, as stated in the previous two chapters as there was a downward trend in rates of hysterectomy being performed by age 53 years this is not a major limitation. Further, any effect of hysterectomy on psychological health appears to be restricted to hysterectomies performed earlier in adulthood rather than later.

In analyses both of psychological health and self-perceptions of hysterectomy it is possible that bias was introduced due to the necessary exclusion of women who had missing data on important variables. However, as discussed above, bias does not appear to be a major problem in analyses of self-perceptions of hysterectomy and in comparisons of the psychological health at age 36 and 53 years of those women for whom hysterectomy status was known with those women for whom it was missing there were no significant differences.

Only information which has been collected can be included in analyses. It is possible that other important factors such as complications during surgery, long recovery time, level of perceived involvement in decision to undergo hysterectomy and persistence of symptoms all affect women's perceptions of the effect of their hysterectomy and could explain the associations found between other factors and self-perceived effects of hysterectomy in this chapter, however, such factors cannot be examined as this information is not known.

11.6.5 Strengths

The major strengths of these analyses are that they examined the long-term association between hysterectomy and psychological health, variation in effect by a range of potentially important characteristics of hysterectomy and adjusted for potentially important confounders prospectively collected across life. This has been done using a cohort who remain, despite losses to follow-up, fairly nationally representative whereby it may be possible to generalise the results from this study to other women born at a similar time in the UK.

It has also been possible to examine women's own perceptions of the effect of their hysterectomies and explore a wide range of factors which may affect these so that women at most risk of suffering from negative perceptions can be identified.

11.6.6 Conclusions and implications

These analyses have identified a potentially important association between young age at hysterectomy and subsequent psychological health, have confirmed the detrimental effect on psychological health of having a hysterectomy for cancer and demonstrated that most women perceive that there is a positive overall effect of hysterectomy on their quality of life and wellbeing.

The poor psychological health of women who had undergone hysterectomy for cancer suggests that these women may not be receiving sufficient support to deal with the psychological trauma of being diagnosed with and treated for cancer.

It is not possible from these analyses alone, given all women are the same age, to identify whether there is an age or period effect operating which explains the association between young age at hysterectomy and subsequent psychological health in the NSHD. That a significant association has been found reignites the debate about whether there is an association between hysterectomy and psychological health which most recent investigators had concluded was unlikely to exist. Further investigation of this association among cohorts of women born at different times is required given the apparent robustness of the association in the NSHD and the potentially important implications of such an effect being real.

Onset and timing of vasomotor symptoms appear to be important to women and affect their perceptions of the effect of hysterectomy and psychological health. Analyses suggest that further investigation of the association between hysterectomy, ovarian failure and onset of vasomotor symptoms is necessary given the significance which these outcomes appear to have for women. Separating out the independent effect of hysterectomy from oophorectomy is especially important as this could have implications for the future use of prophylactic oophorectomies as well as hysterectomies. Investigating the association between hysterectomy, ovarian failure and symptom experiences is also important given it is not possible at present to identify whether women who undergo hysterectomy especially at a young age have increased risk of early menopause independent of hysterectomy status (because hysterectomy is acting as a sign of early ageing) or whether early onset of ovarian decline is caused by hysterectomy and therefore could be avoided by delaying the procedure.

Table 11.1: Means and unadjusted differences in mean $\log_e$(GHQ-28) scores at age 53 years by hysterectomy status in the NSHD

Hysterectomy status	N	Mean (SD) Median GHQ-28 score	GHQ-28 score > 4 N (%)	$\log_e$(GHQ-28) Regression coefficient (95% CI)
No hysterectomy or oophorectomy	1115	3.04 (4.78) 1	271 (24.3)	0.00
Hysterectomy*	310	3.54 (5.38) 1	81 (26.1)	0.09 (-0.04, 0.21)
Oophorectomy only†	20	3.65 (6.68) 1.5	3 (15.0)	0.05 (-0.38, 0.49)
Total	1445	3.16 (4.95) 1	355 (24.6)	
p-value (F test)				0.37

* with or without oophorectomy
† bilateral or unilateral

Table 11.2: Means and unadjusted differences in mean log_e(GHQ-28) scores at age 53 years by characteristics of hysterectomy in the NSHD

Characteristic of hysterectomy	Total N	Mean (SD) Median GHQ-28 score	GHQ-28 score > 4 N (%)	log_e (GHQ-28) Regression coefficient (95% CI)
No hysterectomy or oophorectomy	1115	3.04 (4.78) 1	271 (24.3)	0.00
Hysterectomy with oophorectomy	165	3.38 (5.22) 1	42 (25.5)	0.06 (-0.10, 0.22)
Hysterectomy no oophorectomy	145	3.73 (5.57) 1	39 (26.9)	0.12 (-0.05, 0.29)
Oophorectomy only	20	3.65 (6.68) 1.5	3 (15.0)	0.05 (-0.38, 0.49)
p-value				*0.61*
No hysterectomy or oophorectomy	1115	3.04 (4.78) 1	271 (24.3)	0.00
Hysterectomy for: Fibroids	104	2.95 (4.91) 1	24 (23.1)	-0.05 (-0.25, 0.14)
Menstrual disorders	99	3.82 (5.29) 1	30 (30.3)	0.16 (-0.04, 0.36)
Prolapse	26	3.12 (5.67) 1	6 (23.1)	-0.04 (-0.42, 0.34)
Cancer	18	5.33 (5.94) 3	7 (38.9)	0.49 (0.04, 0.95)**
Other reasons	47	3.83 (6.15) 2	11 (23.4)	0.16 (-0.13, 0.45)
Unknown reasons	16	3.56 (5.53) 1.5	3 (18.8)	0.10 (-0.38, 0.59)
p-value				*0.26*
No hysterectomy or oophorectomy	1115	3.04 (4.78) 1	271 (24.3)	0.00
Route of hysterectomy: Abdominal	236	3.50 (5.29) 1	62 (26.3)	0.08 (-0.06, 0.22)
Vaginal	56	3.13 (5.39) 1	13 (23.2)	-0.02 (-0.28, 0.24)
Unknown	18	5.50 (6.38) 2.5	6 (33.3)	0.54 (0.08, 1.00)**
p-value				*0.10*
No hysterectomy or oophorectomy	1115	3.04 (4.78) 1	271 (24.3)	0.00
Age at hysterectomy (years): < 40	86	4.94 (6.25) 2	33 (38.4)	0.35 (0.14, 0.57)**
40 - 44	82	2.79 (4.54) 1	16 (19.5)	-0.04 (-0.26, 0.18)
45 - 49	97	3.20 (5.40) 1	20 (20.6)	-0.003 (-0.21, 0.20)
≥50	45	3.00 (4.58) 1	12 (26.7)	0.01 (-0.28, 0.30)
p-value				*0.03*
No hysterectomy or oophorectomy	1115	3.04 (4.78) 1	271 (24.3)	0.00
Pre-menopausal hysterectomy	303	3.62 (5.42) 1	81 (26.7)	0.11 (-0.02, 0.23)
Post-menopausal hysterectomy	7	0.29 (0.76) 0	0 (0)	-0.72 (-1.44, 0.01)
p-value				*0.03*

** $p < 0.05$

Note: p-values from likelihood ratio test comparing model with categorisation of hysterectomy shown with a model in which all hysterectomies were grouped together (women with oophorectomy only excluded from all models except those examining oophorectomy status)

Table 11.3: Differences in mean $\log_e$(GHQ-28) scores at age 53 years by age at hysterectomy adjusted for individual sets of variables in the NSHD
(Women excluded if hysterectomy occurred at age ≥53 years or if hysterectomy was performed for cancer)

Variable/s adjusted for:	Regression coefficient (95% CI)				p-value
	No hysterectomy	Age at hysterectomy (years)			
		< 40	40-49	≥50	
Prior psychiatric state (N=1372)					
Unadjusted	0.00	0.39 (0.16, 0.62)	-0.07 (-0.23, 0.09)	0.03 (-0.27, 0.33)	0.005
Adjusted	0.00	0.35 (0.13, 0.57)	-0.08 (-0.23, 0.08)	0.03 (-0.27, 0.32)	0.01
Maternal neuroticism (N=1197)					
Unadjusted	0.00	0.30 (0.06, 0.55)	-0.02 (-0.19, 0.15)	0.06 (-0.27, 0.39)	0.10
Adjusted	0.00	0.30 (0.06, 0.54)	-0.04 (-0.21, 0.13)	0.06 (-0.27, 0.39)	0.09
Parental divorce (N=1407)					
Unadjusted	0.00	0.35 (0.12, 0.57)	-0.05 (-0.21, 0.10)	0.01 (-0.29, 0.30)	0.02
Adjusted	0.00	0.34 (0.12, 0.56)	-0.05 (-0.20, 0.11)	0.02 (-0.28, 0.31)	0.02
Cognition at age 8 years (N=1259)					
Unadjusted	0.00	0.38 (0.14, 0.61)	-0.04 (-0.21, 0.13)	0.02 (-0.31, 0.34)	0.01
Adjusted	0.00	0.38 (0.14, 0.61)	-0.04 (-0.21, 0.12)	0.01 (-0.32, 0.33)	0.01
Lifetime SEP (N=1142)					
Unadjusted	0.00	0.37 (0.11, 0.63)	0.001 (-0.18, 0.18)	0.01 (-0.33, 0.35)	0.05
Adjusted	0.00	0.38 (0.12, 0.64)	0.001 (-0.18, 0.18)	0.002 (-0.34, 0.34)	0.04
BMI at 26 years (N=1230)					
Unadjusted	0.00	0.32 (0.07, 0.56)	-0.10 (-0.27, 0.06)	0.08 (-0.24, 0.40)	0.03
Adjusted	0.00	0.31 (0.07, 0.56)	-0.10 (-0.27, 0.07)	0.08 (-0.24, 0.40)	0.04
Smoking status at age 36 years (N=1288)					
Unadjusted	0.00	0.36 (0.13, 0.59)	-0.06 (-0.23, 0.10)	0.05 (-0.25, 0.36)	0.01
Adjusted	0.00	0.35 (0.12, 0.58)	-0.06 (-0.22, 0.10)	0.05 (-0.25, 0.36)	0.02
Hormone replacement therapy use (N=1407)					
Unadjusted	0.00	0.35 (0.12, 0.57)	-0.05 (-0.23, 0.10)	0.01 (-0.29, 0.30)	0.02
Adjusted	0.00	0.30 (0.08, 0.53)	-0.07 (-0.24, 0.09)	0.01 (-0.30, 0.31)	0.04

Table 11.4: Unadjusted associations between potential explanatory factors and self-perceived effect of hysterectomy on quality of life and wellbeing (Total N=316)

	Effect of hysterectomy on quality of life and wellbeing N(row %)			p-value*	Relative risk (95% CI) of:	
	Very good or good	Neither good nor bad	Bad or very bad		perceiving neither a good nor a bad effect	perceiving a bad or very bad effect
Total	265 (83.9%)	37 (11.7%)	14 (4.4)			
Concomitant unilateral or bilateral oophorectomy No	131 (87.9)	15 (10.1)	3 (2.0)	0.09	1.00	1.00
Yes	134 (80.2)	22 (13.2)	11 (6.6)		1.43 (0.71, 2.88)	3.58 (0.98, 13.14)
Reason for hysterectomy Benign	252 (85.7)	29 (9.9)	13 (4.4)	<0.001	1.00	1.00
Cancer	10 (52.6)	8 (42.1)	1 (5.3)		6.95 (2.54, 19.01)	1.94 (0.23, 16.31)
Age at onset of vasomotor symptoms (yrs) ≥46	125 (88.7)	12 (8.5)	4 (2.8)	0.001	1.00	1.00
41 – 45	80 (87.9)	9 (9.9)	2 (2.2)		1.17 (0.47, 2.91)	0.78 (0.14, 4.36)
≤40	13 (56.5)	7 (30.4)	3 (13.0)		5.61 (1.88, 16.74)	7.21 (1.45, 35.80)
GHQ-28 score at age 53 years 0 – 4	180 (85.3)	24 (11.4)	7 (3.3)	0.004	1.00	1.00
5 – 13	45 (84.9)	7 (13.2)	1 (1.9)		1.17 (0.47, 2.88)	0.57 (0.07, 4.76)
14 – 28	12 (66.7)	2 (11.1)	4 (22.2)		1.25 (0.26, 5.93)	8.57 (2.20, 33.41)

* p-value from chi-squared test

Note: Total N for analyses of different explanatory factors varied due to missing data

Table 11.5: Adjusted associations between potential explanatory factors and self-perceived effect of hysterectomy on quality of life and wellbeing (N=231)

		Unadjusted relative risk (95% CI) of:		Adjusted relative risk (95% CI) of:	
		perceiving neither a good nor a bad effect	perceiving a bad or very bad effect	perceiving neither a good nor a bad effect	perceiving a bad or very bad effect
Concomitant unilateral or bilateral oophorectomy	No	1.00	1.00	1.00	1.00
	Yes	1.76 (0.74, 4.17)	7.92 (0.97, 64.5)	1.64 (0.67, 4.02)	7.69 (0.91, 65.2)
	p-value		*0.03*		*0.05*
Reason for hysterectomy	Benign	1.00	1.00	1.00	1.00
	Cancer	5.17 (1.40, 19.13)	3.39 (0.37, 30.97)	5.25 (1.30, 21.19)	2.29 (0.21, 25.36)
	p-value		*0.06*		*0.09*
Age at onset of vasomotor symptoms (yrs)	≥46	1.00	1.00	1.00	1.00
	41 – 45	1.34 (0.52, 3.45)	0.74 (0.13, 4.16)	1.28 (0.48, 3.38)	0.63 (0.10, 4.01)
	≤40	5.08 (1.59, 16.26)	6.35 (1.28, 31.54)	4.65 (1.40, 15.44)	5.03 (0.85, 29.89)
	p-value		*0.03*		*0.06*
GHQ-28 score at age 53 years	0 – 4	1.00	1.00	1.00	1.00
	5 – 13	1.34 (0.50, 3.62)	no women in category	1.39 (0.49, 3.91)	no women in category
	14 – 28	0.75 (0.09, 6.17)	6.77 (1.49, 30.82)	0.60 (0.07, 5.42)	6.51 (1.18, 35.82)
	p-value		*0.05*		*0.05*

Chapter 12: Hysterectomy: Its predictors and health consequences

12.1 Summary of main findings

This thesis has identified some important predictors and long-term health consequences of hysterectomy in a British birth cohort. Educational level and age at menarche were inversely associated with hysterectomy in the NSHD, the former of these associations attenuated with age. Parity was positively associated with hysterectomy - women who had three or more children experienced higher rates of hysterectomy than women with fewer or no children. Body weight in adulthood was also associated with subsequent hysterectomy rates with a suggestion that increasing weight across adulthood was associated with increased risk of subsequent hysterectomy. Women who reported having suffered from irregular/infrequent menstrual cycles a lot during their 20s and/or 30s also had much higher rates of hysterectomy than other women. These associations were all largely independent of each other and there was evidence of biological and social pathways operating via medical need and supply and demand factors to hysterectomy.

The relationship between the above factors and hysterectomy appeared to be responsible for the slightly higher subsequent BMI in middle-age of hysterectomised women in the NSHD compared to other women. While the hysterectomised women in the NSHD also had higher risk profiles for the other health outcomes studied, musculoskeletal and psychological health, there was some evidence that women who had hysterectomies before age 40 years had elevated risk of poor musculoskeletal and psychological health even when their higher pre-hysterectomy risk profiles had been taken into account. Women who had hysterectomies at later ages had no higher risk of subsequent poor musculoskeletal or psychological health than women who had not undergone hysterectomy or oophorectomy. There may therefore be a particularly harmful direct effect on subsequent health of having a hysterectomy at a young age. It is also possible that there was a period effect operating which explains these findings or, hysterectomy at a young age could be a manifestation of early ageing.

The majority of women in the NSHD perceived that their hysterectomy had had a beneficial effect on their quality of life and wellbeing. Factors associated with negative perceptions of the effect of the procedure were poor psychological health, early onset of vasomotor symptoms and concomitant oophorectomy.

As well as improving our understanding of the predictors and long-term health consequences of hysterectomy which has important implications, this thesis has generated areas for future research in the NSHD and other study populations.

12.2 Relevance of thesis

The public health importance of hysterectomy and the continued need to improve our knowledge of the epidemiology of this procedure was highlighted by the inclusion of hysterectomy in the UK's Chief Medical Officer (CMO), Sir Liam Donaldson's annual report for 2005, 'On the State of Public Health'[107] which was reported widely in the media.[515-517] The increasing funding pressures within the NHS have made it necessary to examine the use of treatments performed within the UK, especially those which were introduced before the revolution in evidence-based medicine. The CMO argues that regional variations in both rates of hysterectomy and declines in hysterectomy rates for menstrual disorders suggest that provision of hysterectomy is inequitable and may be overused. He suggests that millions of pounds could be saved if hysterectomy rates were reduced to the same levels recorded in the areas of the UK with the lowest rates across all areas of the country. To address this there is a need to increase the evidence-base of knowledge about hysterectomy and other treatments in order to produce appropriate guidelines for doctors to follow. This thesis can contribute to improving the evidence-base.

The results from this thesis are also of relevance as they address the wider research need to study the determinants and sequelae of health conditions which do not limit life or directly cause death but which affect quality of life, wellbeing, ageing and health spending. Studying such conditions is becoming an increasing research priority as populations age. While people in current generations are living longer lives than their predecessors, they are not necessarily healthier.[518]

As epidemiological methods advance, these need to be applied to address long-standing debates which it has not been possible to resolve. When novel approaches are introduced it is not possible to know how useful they will be. This thesis applied a life course approach to the study of a health outcome which, unlike many other health outcomes previously studied using this approach, does not have its own aetiology and is instead determined by aetiological pathways to gynaecological conditions (i.e. medical need) and also by psycho-social pathways to supply of and demand for hysterectomy.

12.3 Implications of findings

12.3.1 The predictors of hysterectomy

The identification of a range of pathways operating between factors in earlier life, mainly in earlier adulthood, and hysterectomy suggests that the determination of hysterectomy risk is complex. There were a number of associations identified which suggest that hysterectomy in the NSHD was associated with medical need. This is what would be hoped for and should have been found if treatment matched need and was equitable. These were: the presence of an association between age at menarche and hysterectomy which appeared, from the available evidence, to be operating on a biological pathway; and the presence of an association between irregular/infrequent menstrual cycles and hysterectomy. There was also some evidence to suggest that the associations between BMI in adulthood and hysterectomy and between educational level and hysterectomy may be partially explained by pathways operating to influence medical need. However, there was also evidence that some factors i.e. education and parity were operating at least partially through direct influences on supply and demand factors. One reason for finding associations which acted on supply and/or demand could be that the treatment women received was to some extent inequitable, although this is not the only plausible reason. It is not possible from the results in this thesis to identify whether women with higher levels of education and lower parity had lower risk of hysterectomy because they were less likely to seek treatment for gynaecological conditions (either because they were less likely to develop gynaecological conditions or less likely to feel that their condition required medical treatment) than women of lower educational levels and higher parity, or whether women of all educational levels and all levels of parity were equally likely to seek medical treatment for gynaecological conditions but that the medical advice and treatment they received was different. Only the latter of these would suggest inequitable treatment and so further research is needed to address which of these situations was operating. Further, the presence of an association between parity and hysterectomy which appears to be operating via its influence on supply and demand does not necessarily suggest poor or inequitable treatment. If all women were able to make their own fully informed choices about treatment, as would be hoped, an association with parity such as has been found could exist because loss of fertility is an important consideration for women when making their treatment choices.

Given there are a range of factors which predict hysterectomy risk, some of which do appear to act to influence medical need, some variation in hysterectomy rates across areas of the UK should be expected even if treatment is equitable. This is because it is unlikely that risk factors for gynaecological conditions and therefore medical need for hysterectomy are equally distributed across the country.

How applicable the results on the predictors of hysterectomy in the NSHD are to other populations especially younger generations may be questioned given recent declines in hysterectomy rates,[101] the introduction of alternative treatments and other changes which have occurred over time. However, as hysterectomy was one of the only viable treatments for women experiencing gynaecological symptoms in the NSHD especially in earlier adulthood, it is likely that hysterectomy in the NSHD is an indicator of gynaecological treatment overall. Therefore, the factors found to predict hysterectomy risk in the NSHD may be those factors which predict gynaecological treatment overall in younger populations, although in younger populations women who have received gynaecological treatment are likely to be distributed across a wider range of different treatment outcomes.

12.3.2 Long-term health consequences of hysterectomy

A striking finding of this thesis was that women who had undergone hysterectomy before age 40 years had poorer musculoskeletal and psychological health at age 53 years than other women. This has potentially important implications. The implications of these findings are however dependent on the explanation of these findings which it has not been possible to elucidate using the data available. A period effect could explain the findings although this would have to be tested by comparing the results from this thesis to results from similar analyses in other birth cohorts. If it were possible to rule out a period effect, it would then be necessary to consider whether there was a real effect of young age at hysterectomy on subsequent health. If there was a direct detrimental effect of hysterectomy at young ages on subsequent health this would suggest that hysterectomy should only be performed in emergency situations at young ages. If however, hysterectomy at young ages is a manifestation of early ageing this would suggest that women who undergo hysterectomy at a young age are a group of women who require greater levels of advice and support to maintain their existing levels of health and prevent declines in health with age.

Even though the higher BMI at age 53 years of hysterectomised women compared to women who had not undergone hysterectomy or oophorectomy did not appear to be due to a direct effect of hysterectomy on subsequent BMI, the higher risk profile for poorer health outcomes among hysterectomised women which explained this association suggests that hysterectomised women are a group of women who require greater levels of support and advice to maintain good health with age.

Another striking finding of this thesis was that the majority of hysterectomised women in the NSHD perceived that their hysterectomy had a positive effect on their quality of life and wellbeing. This finding and the women's accompanying comments, suggest that gynaecological conditions are a major public health problem as they have detrimental effects on women's quality of life and wellbeing. This is highlighted most clearly by the fact that even women who anecdotally reported detrimental consequences of hysterectomy reported that their hysterectomy overall had a positive effect as it removed the gynaecological symptoms from which they were suffering and which were affecting their daily activities. Gynaecological conditions represent a large percentage of demand for medical care especially among women in early and mid-adulthood. Given the effects which suffering from these conditions appear to have on women and the benefit which can be provided by removing them there is clearly a need to provide some form of treatment and relief from gynaecological symptoms for women. If hysterectomies are to be discouraged as the CMO suggests, other treatments which are equally effective at improving women's subsequent quality of life and wellbeing are required.

Even if hysterectomy becomes obsolete in future years it is important to understand the health consequences of this surgical procedure. Given the high prevalence of hysterectomy in current generations of women reaching middle- and old-age, hysterectomy is a potentially important factor in trying to understand the variation in risk of other subsequent health outcomes in these populations. Further, an appropriate comparison between hysterectomy and alternatives cannot be performed unless the long-term costs and benefits of all procedures are known.

12.3.3 Life course epidemiology

This thesis has demonstrated that a life course approach can be applied to the study of health outcomes such as hysterectomy, which in the strictest sense of the definition do not have their own aetiology and which may be directly influenced by both biological and social pathways. Not only can this approach be used but it is informative. While none of the main predictors of hysterectomy identified in thesis were operating earlier in life than menarche the study of factors such as SEP and BMI across life enabled the associations to be examined in more detail than has been achieved previously and allowed elucidation of the pathways which were most likely to underlie the observed associations.

The analyses of associations between hysterectomy and subsequent health outcomes demonstrate that a life course approach is illuminating even when both the outcome and main explanatory variable are in adulthood and that inappropriate conclusions may be reached if early life factors are not considered in analyses such as these.

12.4 Strengths and limitations

A number of strengths and limitations of the work presented in this thesis have been discussed in previous chapters and so will not be repeated here. Other more general strengths and limitations are discussed. Many of these relate to the extent to which this study has managed to limit the possibility that the findings of analyses were due to chance, reverse causality, bias or confounding, major considerations in any observational epidemiological study.

The prospective nature of the majority of data collection, the fact that the data used were not collected specifically for these analyses and study members and interviewers were unaware of the hypotheses being tested in this thesis are major strengths. As a result, the main exposure variables are unlikely to have been differentially misclassified by outcome status and vice versa. Any misclassification of variables is therefore expected to have been random and would not be expected to have introduced bias. The nature of the data also enabled the establishment of a clear temporal relationship between explanatory variables and outcomes whereby all results presented in this thesis are unlikely to be due to reverse causality. However, the study of the predictors of hysterectomy may be limited as it was not possible to ensure that the predictors examined, as well as occurring before hysterectomy, also occurred before the development of gynaecological conditions.

While a major strength of analyses in this thesis was the availability of data from across life collected prospectively by trained professionals, some of the main variables of interest i.e. hysterectomy and oophorectomy status, timing of hysterectomy and route of procedure were self-reported retrospectively. These variables may therefore be less valid and using them may have introduced bias. Hysterectomy status and timing of hysterectomy were not ascertained for the first time until age 43 years. While this does mean early hysterectomies were self-reported by recall, after age 43 years the information on hysterectomy was collected regularly and, during the time when most hysterectomies occurred i.e. while women were in their late 40s and early 50s, recall was limited to no more than one year as women were asked about their hysterectomy status annually. Route of hysterectomy had a greater recall length as it was not asked about for the first time until women were aged 51 years. Despite the fact that these data were self-reported retrospectively, the similarities between the prevalence of hysterectomy, the age distribution of hysterectomy and the distribution of different routes of procedure in the NSHD compared to other UK study populations, as described in chapter 2, does suggest that these data were valid. Further, only two (0.6%) of 322 women who were sent and returned the reasons for hysterectomy questionnaire in 2005 reported not having had a hysterectomy in their response to this new questionnaire, all other women confirmed their hysterectomy status. While it was not possible to verify all self-reported information on hysterectomy in the NSHD by comparison to medical records, a number of other studies have done this.[128;271;519-523] These have found that surgical procedures in general, hysterectomy, timing of hysterectomy, oophorectomy status and route of procedure are all accurately self-reported and not differentially misclassified by important factors. One study[519] examined the differences in association between hysterectomy and various explanatory variables when using self-reported hysterectomy status compared to hospital recorded hysterectomy and found that analyses using self-reported hysterectomy were not biased and valid results were obtained by both methods. This suggests that the use of self-reported retrospective hysterectomy measures was not a major limitation of analyses in this thesis.

As hysterectomy status was not ascertained for the first time until age 43 years female cohort members who had died, previously refused to participate or been lost before this age had to be excluded from analyses. While the NSHD were originally selected to be nationally representative these losses to follow-up could have introduced bias. While there was some evidence from analyses, comparing those female members of the cohort included in analyses to those excluded, to suggest that female cohort members who were lost i.e. not included in analyses were more likely to have been of lower SEP and to have had higher parity very few other factors examined were associated with loss to follow-up. Although the hysterectomy status of those women not followed-up cannot be examined there is no reason to believe that the prevalence of hysterectomy would be different and that the associations found would differ if there had been no losses to follow-up. This is therefore unlikely to have been a major source of bias.

Exclusion of those women who had data on hysterectomy status but who had missing data on important explanatory variables in chapters 4 to 7 or on outcome variables in chapters 9 to 11 were also made in analyses. While data are not expected to be missing completely at random there is no reason to believe that data were missing differentially by hysterectomy status whereby these exclusions are unlikely to have introduced bias and, the associations found between hysterectomy and the explanatory and outcome variables examined are expected to be valid.

The method of managing missing data used in this thesis could be criticised as methods do exist to impute missing data.[524-526] However, as one of the assumptions made when imputing missing data is that data is missing at random the method employed in this thesis, which is commonly used by many researchers, may have been the most appropriate.

The exclusion of women from analyses reduced the sample size available for analysis. The sample size could have limited the ability to rule out the possibility that results found were due to chance. In all analyses, the role of chance in explaining the associations found was considered by examining p-values and 95% confidence intervals. All those associations which have been highlighted as important findings of this thesis were statistically significant at the 5% level and so are unlikely to be explained by chance. Other important associations, for example, variations in associations between predictors and hysterectomy by reason and variations in associations between hysterectomy and subsequent health outcomes by characteristics of hysterectomy may have gone undetected because of insufficient power to detect the levels of effect which exist.

The range of data available from across life was also of benefit as it enabled potential confounders and effect modifiers to be included in analyses whereby the possibility that results were due to confounding was minimised. That the cohort are all the same age also limited the possibility of confounding as age and other potentially important factors such as social and cultural changes (for example, the introduction of oral contraceptives) were constant i.e. experienced by the women at the same age.

While the fact that the NSHD are all the same age has benefits it does also unfortunately limit the generalisability of some of the results and limits our understanding of some of the other associations found. There have been many changes in factors relevant to hysterectomy over time including changes in: women's social roles; medical practice; patient autonomy; childbearing; HRT and OC use; levels of overweight and obesity; and the availability of alternatives to hysterectomy. That women from different birth cohorts have experienced these potentially important changes at different ages could mean that the predictors of hysterectomy identified in this cohort may not be associated with hysterectomy in the same way in other birth cohorts, as exemplified by the findings from comparisons of the association between SEP and hysterectomy across three cohorts reported in chapter 4. This need not be a limitation of all analyses as any real and direct effect of hysterectomy on subsequent health would be expected to be found across birth cohorts.

Although there are some limits to the generalisability of results, the national representativeness of the original cohort, the fact that the cohort is population-based rather than, as in many studies of women's health, clinic- or hospital-based, and that confounding and bias were minimised does mean that all the results from this study should be more generalisable than results from many other studies.

As demonstrated above, using such a large, well established prospective study to perform analyses does have major benefits. However, there was a limit to how much relevant information related specifically to hysterectomy was available in the NSHD. During each data collection, data has to be collected on a wide range of factors including various health measures. The amount of information collected at any one time about any one specific research interest has to be compromised as study participants cannot be expected to answer all possible questions and perform all the potential tests as would be required to examine all research interests to the same high level of detail. Not only can study participants not be asked too many questions or asked to perform too many medical tests at any one time but they can also not be exposed to data collections too often or loss to follow-up would increase. Further, while the prospective nature of data collection is a major strength it does mean that current researchers are restricted to using data previous investigators thought it was appropriate to collect at the time of collection. As scientific theories have advanced since the data from earlier in life was collected the measures which it would now seem most appropriate to use may not have been collected. The result of this is that: it was not possible to examine the underlying processes which led to hysterectomy and to identify those women in the NSHD who sought treatment for gynaecological conditions but did not accept or did not get offered a hysterectomy; there was no information available to be able to examine the differences in consequences of hysterectomy by other characteristics of hysterectomy (such as whether the hysterectomy was total or sub-total); and it was not possible to examine the consequences of hysterectomy in relation to the complications women suffered during and immediately after surgery. These, however are not major limitations of the study as much relevant information was available and the major benefits of the dataset outweigh minor limitations such as these.

Further important strengths of this study compared to others include the fact that it has been possible to look at variations in association by reason and age at hysterectomy and include variables in analyses from across life. This thesis has tried to examine a contentious issue from a neutral position, independent of any ulterior interest in protecting the reputation of gynaecological medicine or feminist theories.

12.5 Future work

The results from this thesis suggest many areas for further research. In chapter 7 details of the further research of the predictors of hysterectomy which could be pursued were described. In summary it is suggested that other potential predictors of hysterectomy, including genetic factors, childhood cognition and health care seeking behaviour, should be investigated. These may all prove to be important, independent predictors of hysterectomy and they may also be related to the predictors already identified and therefore provide further elucidation of the pathways underlying these associations. The pathways most likely to explain the associations between predictors and hysterectomy could be formally tested using statistical techniques such as structural equation modelling. In addition to further work using data from the NSHD, comparative analyses should be performed to identify the similarities and differences between the predictors of hysterectomy risk in other birth cohorts of women within the UK and in cohorts from other countries given the possibility of marked variation over time and place. Larger study populations could also be used to examine the variation in associations found by reason for hysterectomy which there was insufficient power to study in any detail in the NSHD but which there was evidence to suggest may exist.

With regards to the study of the health consequences of hysterectomy, there is a need to examine other potential health consequences of hysterectomy, taking into account factors from across life which could predict both hysterectomy and the outcome under study as was done in this thesis. Such outcomes include incontinence, cancer, CVD, cognition in adulthood and perhaps most importantly given the apparent significance of the outcome to women, ovarian ageing and vasomotor symptoms. After future data collections it will be possible to examine not only absolute levels of health outcomes but also rates of change in these and to examine whether hysterectomised women are at increased risk of greater declines in health status that occur with age. It will also be possible in the future to examine whether the small differences in BMI and physical performance measures between hysterectomised and non-hysterectomised women found at age 53 years manifest into significant differences in levels of clinical outcomes such as CVD and osteoporosis at later ages.

There is a clear need to investigate further the elevated risk of poor health which appears to be experienced by women who had hysterectomies at young ages in the NSHD. As well as investigating whether the same effect is found when examining other potential health outcomes in the NSHD it is necessary to examine whether the same effect is found in other birth cohorts. By comparison with other cohorts it would be possible to identify whether the results are due to a period effect or not. If they are not due to a period effect then the possibility that hysterectomy at a young age is a manifestation of early ageing should be investigated further. The role of hysterectomy compared to other potential markers of reproductive and general ageing such as sub- and infertility and early natural menopause should be investigated.

As well as improving our understanding of the epidemiology of hysterectomy, there is a need to improve our understanding of the epidemiology of gynaecological conditions. The level to which hysterectomy and other treatments match need cannot be fully assessed unless we understand the overlap between the factors which predict hysterectomy and other treatments and the factors which predict the development and severity of gynaecological conditions. Further, if we want to reduce the number of women undergoing hysterectomy we need to look at ways not only of increasing the use of less radical alternatives but also of reducing the number of women who have a need for any gynaecological treatment. This can only be achieved by identifying modifiable risk factors of gynaecological conditions. A reduction in the incidence of gynaecological conditions and the severity of these would not only reduce the amount of female suffering but would reduce the demands placed on the health service by these conditions and so reduce health spending, which is not a guaranteed result of promoting the use of alternative treatments. It is also possible that the higher risk of poorer health which women who undergo hysterectomies appear to experience may also be avoided if the development of gynaecological conditions could be prevented.

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Appendices

Appendix 1: Letter and questionnaire sent to study participants

Medical Research Council

MRC National Survey of Health and Development
Royal Free & University College Medical School
Department of Epidemiology and Public Health
1-19 Torrington Place
London WC1E 6BT

PRIVATE AND CONFIDENTIAL

[Cohort member's name and address]

Dear [cohort member]

Please find enclosed a short postal questionnaire which we would appreciate you taking a few minutes to complete. We need a small amount of further information about any operations you may have had to remove your uterus and/or ovaries and the reasons why these were performed, so that we can continue our research on this. You may already have provided some of the information we are asking you for but we would be very grateful if you could provide us with this again so that we can confirm the information we already have, and ensure that nothing is missing.

When you have completed the questionnaire please use the pre-paid envelope provided to post it back to us.

If you have not had your uterus or ovaries removed please answer only question one and then return the questionnaire to us.

We look forward to hearing from you. Thank you for your help and cooperation.

Yours sincerely

Diana Kuh PhD

M E J Wadsworth PhD
Director of the study

STRICTLY CONFIDENTIAL

MRC NATIONAL SURVEY OF HEALTH AND DEVELOPMENT
University College London Medical School
Department of Epidemiology and Public Health
1 – 19 Torrington Place
London WC1E 6BT

WOMEN'S HEALTH IN THE MIDDLE YEARS
(HYSTERECTOMY STUDY)

Postal questionnaire 2005

When completing the questionnaire please use a pen to circle the appropriate response to each question. Please feel free to add any further explanations or comments which will help us to understand your particular experiences.

You may already have provided some of the information we are requesting in an earlier postal questionnaire or during a home visit. As we are collecting the information in more detail this time we would be very grateful if you would provide the information again so that all women in the survey will have answered the same questions.

All information you provide will be treated in the strictest confidence. If you have any queries please do not hesitate to telephone Suzie Butterworth on 020 7679 5642 or write to us at the above address.

When you have completed the questionnaire please use the pre-paid envelope provided to post it back to us. Thank you very much for your time and cooperation.

Address (if different from the one we have used)

____

____

____

____

____

Postcode____________________________

Please give the date you completed this questionnaire:

_______day __________ month 20______

1. Have you ever had an operation to remove your uterus (womb) and/or ovaries? No 0

Yes 1

If *no* please do not answer any further questions.

2. What did the doctor tell you at the time were the reasons for removing your uterus and/or ovaries?

	Main reason (*circle one*)	Other reasons (*circle all that apply*)
Heavy periods	1	1
Painful periods	2	2
Fibroids	3	3
Endometriosis	4	4
Prolapse	5	5
Pelvic inflammatory disease	6	6
Ovarian cysts	7	7
Uterine (womb) cancer (*this includes endometrial cancer)*	8	8
Cervical cancer	9	9
Ovarian cancer	10	10
Other cancer, please specify site________________________ ____	11	11
Other reason, please specify__________________________ ____	12	12

3. If you have had an operation to remove your uterus what type of hysterectomy did you have?

Abdominal hysterectomy 1
(the uterus (womb) was removed through a single cut made in the lower part of the tummy)

Vaginal hysterectomy 2
(the uterus was removed through the vagina)

Other, please specify 3

____

Not sure 9

Did not have a hysterectomy 0

4. In order that we can update our records on recent hysterectomies and oophorectomies please give dates of all operations *performed in 2002 or later*. If you cannot remember the month and year, give your age at the time of the operation. If your operation was *performed before 2002* please go straight to question 5.

	No	Yes	Month/Year	Age (yrs)
a) Removal of uterus (womb) and both ovaries (hysterectomy and bilateral oophorectomy)	0	1	☐☐ ☐☐☐☐	☐☐
b) Removal of uterus (womb) only (hysterectomy)	0	1	☐☐/☐☐☐☐	☐☐
c) Removal of uterus (womb) and one ovary (hysterectomy and oophorectomy)	0	1	☐☐/☐☐☐☐	☐☐
d) Removal of both ovaries only (bilateral oophorectomy)	0	1	☐☐/☐☐☐☐	☐☐
e) Removal of one ovary only (oophorectomy)	0	1	☐☐/☐☐☐☐	☐☐

5. How would you say that the operation to remove your uterus and/or ovaries affected your wellbeing and quality of life? (*circle one*)

Had a very good effect	1
Had a good effect	2
Had neither a good or bad effect	3
Had a bad effect	4
Had a very bad effect	5

6. What were the main ways in which the operation to remove your uterus and/or ovaries affected your wellbeing and quality of life? (*Please specify and continue overleaf if necessary)*

THANK YOU VERY MUCH FOR THE TIME YOU HAVE SPENT FILLING IN THIS QUESTIONNAIRE.

PLEASE RETURN THE QUESTIONNAIRE IN THE PRE-PAID ENVELOPE PROVIDED.

Appendix 2: Summary of studies which have examined the association between socioeconomic position and hysterectomy (listed in chronological order)

Reference	**Study details:** Study design Length of follow-up Study population Country of study Birth cohort/s* N Number of hysterectomies	**Indicator/s of SEP used**	**Definition of hysterectomy used**	**Other variables considered**	**Main findings (Direction of association with hysterectomy: + positive; — negative/inverse; No association)**	**Study limitations**
Bunker and Brown, 1974[147]	•Cross-sectional •NA •Women in specific professional groups or women married to men in specific professional groups in California •USA •Not known •Not reported •Not reported	Professional status (Doctor; lawyer; wife of a doctor; wife of a protestant minister; wife of a lawyer; wife of a businessman)	Not reported	Age	Doctor's wives had significantly more hysterectomies than businessmen's wives.	-Not all measures taken in the same way or at the same time -Study population is a restricted socioeconomic group and is not representative of a general population
Koepsell et al, 1980[122]	•Cross-sectional •NA •Women aged 35 to 74 years in 2 urban Washington counties during 1976-77 •USA •1902 - 1942 •1,087 •358	Education; Income	All self-reported hysterectomies	Age, race, marital status, parity, age at first birth, ever had a miscarriage or caesarean, regular menses, other health conditions	Education: — Income: — (but this was only in one of the two counties surveyed and was partially explained by confounding due to age at first birth)	-Wide age range of study participants
Coulter and McPherson, 1985[131] and 1986[184]	•Cross-sectional •NA •Women aged 40 to 64 years randomly selected from 8 Oxford region GP registers •UK •1920 - 1944 •2,160	Occupational class; Age at leaving full time education	All self-reported hysterectomies	Other outcomes: other surgical procedures	Occupational class: — (for NHS operations only but no association in the full sample) Age at leaving education: —	-No control for confounders -Denominator used unclear

	•403					
Meilahn et al, 1989[125]	•Cross-sectional •NA •Women aged 40 to 52 years selected at random from a list of women holding driver's licenses in Pittsburgh, Pennsylvania, in 1983 •USA •1931 - 1943 •2,137 •583	Education	Self-reported hysterectomies with or without oophorectomy or oophorectomy alone for any reason	Current age, age at menarche, age at first birth, race, marital status, parity, cigarette smoking, alcohol consumption, BMI and current religion	Education: —	
Gittelsohn et al, 1991[145]	•Linkage study •NA •Women recorded as having had a hysterectomy in the Maryland hospital discharges for 1985 to 1987 •USA •Not known •Unknown – denominator from analysis from Maryland population estimates •28,891	Median family income of zip code of residence	All recorded hysterectomies	This was a study examining income and race in relation to a range of surgical outcomes	Income: +	-Exposure status assigned at the group level -Denominator estimated so will include women who had already undergone hysterectomy in previous years -No control for confounders
Schofield et al, 1991[114]	•Cross-sectional •NA •Women participants, aged 18 to 69 years, of a community survey of women's health in the Hunter region of New South Wales in 1987-88 •Australia •1918 - 1970 •5,727 •967	Education; Occupational class	All self-reported hysterectomies	Country of birth, parents' countries of birth, marital status, sexual activity and age	Education: — Occupational class: — (Both these associations were maintained after controlling for age)	-Insufficient control for potential confounders
Luoto et al, 1992[123]	•Cross-sectional •NA •Women aged 45 to 64 years old randomly selected from a population census •Finland	Education; Occupational class	Self-reported hysterectomies	Age, parity	Education: — Occupational class: No association	-Insufficient control for potential confounders

	•1925 - 1944 •1713 (86% of those selected) •329					
Santow and Bracher, 1992[127]	•Cross-sectional •NA •Women aged 20 to 59 years •Australia •1927 - 1966 •2,547 •248	Education	All self-reported hysterectomies	Age, parity, marital status, miscarriages, contraceptive failure, oral contraceptive use, sterilisation, religion, place and region of residence, calendar period	Education: —	
Vessey et al, 1992[1]	•Prospective cohort •Up to 21 years •Women in the Oxford Family Planning Association study who were aged 25 to 39 years, married, white and British and a current user of contraception at time of enrollment •UK (England and Scotland) •1929 - 1949 •17,032 •1,885	Husband's occupational class	All recorded hysterectomies	Age, calendar period, parity	Husband's occupational class: no association overall (— for hysterectomies for menstrual problems, 'other' reasons, cancer and pre-cancer. + for hysterectomies for fibroids and endometriosis, not all these associations were statistically significant)	-Women in this cohort were not representative of a national population as they had to be attending a family planning clinic and have consented to taking part in the study
Kjerulff et al, 1993[121]	•Cross-sectional •NA •Women aged 18 years or over who were part of the Behavioral Risk Factor Surveillance System conducted in 16 states •USA •12,465 (7,139 women aged 25 to 54 years on whom main analyses were made) •1934 – 1963 (for women in main analyses) •2,787 (1,287 in women 25 to 54	Education; Income	Self-reported hysterectomies	Age, race	Education: — Income: —	-Insufficient control for confounders

	years)					
MacLennan et al, 1993[124]	•Cross-sectional •NA •Women aged ≥40 years interviewed as part of the South Australian Health Omnibus Survey in October 1991 •Australia •1,047 •292	Education; Household income level	All self-reported hysterectomies	Age, country of birth, BMI, smoking status, alcohol consumption, diabetes, blood pressure, HRT use, mammography attendance and frequency of GP visits	Education: No association Income: No association	-No control for confounders -Crude categorisation of education
Dennerstein et al, 1994[132]	•Cross-sectional •NA •Random sample of Australian born Melbourne women aged 45 to 55 years •Australia •1938 - 1948 •2,001 •420	Education	All self-reported hysterectomies (Women with a uni- or bi-lateral oophorectomy excluded)	Age, age at menarche, pre-menstrual symptoms, number of D&C procedures, number of non-gynaecological operations, use of HRT, smoking, use of prescription medicines	Education: —	
Kuh and Stirling, 1995[133]	•Prospective cohort •Up to 43 years (from birth) •Women born in one week in March 1946 who are members of the MRC NSHD •UK •1946 •1,628 •163 (10% of participants)	Education; Most recent occupational class of self and partner	Hysterectomies as reported in hospital admission reports between the ages of 15 and 43 years	Parity	Education: — Partner's occupational class: — Women's own occupational class: No association	-Insufficient control for confounders -No distinction between hysterectomies for different reasons
Santow, 1995[134]	•Cross-sectional •NA •Female Canberra residents aged 30 to 69 years in 1992 •Australia	Education	Self-reported hysterectomies	Age, parity, tubal sterilisation, caesareans, menstrual problems, country	Education: —	-Small sample size and small number of hysterectomies - Unrepresentative study sample - Crude categorisation of

	•1923 - 1962 •276 •16			of birth		education
Keskimaki et al, 1996[135]	•Linkage study •NA •Women aged 25 years and over listed on the 1987-88 Finnish Hospital Discharge Register •Finland •Not known (upper age limit not reported) •Unknown – denominator derived from 1987 census •17,509	Occupational class; Education; Disposable family income (all obtained from linkage to census data)	Hysterectomies reported in hospital discharge register	Hospital district, age	Occupational class: — Education: — Income: +	-Denominator is an estimate and may have included women who had hysterectomies in previous years -Errors may have occurred in linkage to SEP information -Women treated privately not included in numerator
Settnes and Jorgensen, 1996[136]	•Prospective cohort •Up to 8 years •Women aged 30,40,50 or 60 years selected at random in 1982 •Denmark •1922,1932,1942,1952 •1,765 •183	Education; Own occupational class; Family's occupational class; Social mobility	Hysterectomies for benign diseases (n=155) (pre-malignant and malignant cases excluded (n=28))		Education: — Own occupational class: — Family's occupational class: — (Unemployment and lack of vocational education were associated with hysterectomies for bleeding disorders and uterine fibroids in pre-menopausal women)	-Insufficient control for confounders
Brett et al, 1997[137]	•Prospective cohort •Up to 20 years •Women enrolled in the NHANES I study who were 25 to 49 years old and had not had a hysterectomy at the time of their first examination (1971-75) •USA •1922 - 1950 •4,601 (some of these women excluded) • 1,648	Education; Residence in a poverty census enumeration district	All self-reported hysterectomies which could be confirmed by hospital records	Race, age at first birth, parity, number of miscarriages	Education: Non-linear (women who had attended but did not complete high school were more likely to undergo hysterectomy than women with more or less education) Poverty: No association	-A large proportion of hysterectomy cases were excluded -Poverty status was assigned at the group level
Domenighetti	•Cross-sectional	Professional status	Not reported	Not reported	Female doctors and	-Method unclear

and Casabianca, 1997[148]	•NA •Not described in detail •Switzerland •Not known •1588 •208	(female doctor; wife of a lawyer; professional with a university degree; general population)			lawyer's wives had lower hysterectomy risk than the general population and other female professionals	[NB Meant to be similar to Bunker and Brown paper 1974]
Luoto et al, 1997[138]	•Linkage study •NA •Women who were recorded as having had a hysterectomy in the Finnish hospital discharge register of 1988 •Finland •Not known (age range of women not reported) •Unknown - denominator is all women living in Finland aged 35 years and over in 1988 •8,663	Occupational class; Education; Income (all obtained from linkage to census data)	Hysterectomies reported in hospital discharge register	Age	Occupational class: — Education: — (non-linear) Income: +	-Denominator is an estimate and may have included women who had hysterectomies in previous years -Errors may have occurred in linkage to SEP information
Marks and Shinberg, 1997[139]	•Cohort •Up to 35 years •Women enrolled in the Wisconsin Longitudinal Study •USA •1939 - 1940 •3,326 •1,031	Indicators of childhood SEP : Father's and mother's education; Parents' income and father's occupational class at time of graduation from high school Indicators of adult SEP: Spouse's and own occupational class and income; Education; Family net worth (estimated value of items of personal	Self-reported hysterectomies	Marital status, parity, age at first birth	All indicators of childhood SEP: No association Education: — Spouse's and own occupational class: — Adult income: No association Family net worth: — Home ownership: No association	-Women who had only had an oophorectomy could have been included as hysterectomy cases because of error in wording of questions

		property of family – debt); Home ownership				
Harlow and Barbieri, 1999[120]	•Cross-sectional •NA •Women aged 36 to 44 years listed in the Massachusetts Town Books between 1995 and 1997 and not naturally post menopausal at the time of the study •USA •1951 - 1961 •4,278 •114	Education	All self-reported hysterectomies	Age, race, marital status, BMI, smoking habits, age at menarche, history of irregular menstrual cycles, parity, OC use, history of period pain, endometriosis or uterine fibroids, removal of an ovary	Education: —	-Not clear how much adjustment for confounding was made
Treloar et al, 1999[128]	•Cohort •Up to 14 years •Women enrolled in a nationwide cohort of female twin pairs •Australia •1902 - 1965 •3,096 •524	Education	All self-reported hysterectomies	Age, parity, medical consultation for pelvic pain, problems conceiving, menstrual problems, history of endometriosis, PID or fibroids, previous investigations or interventions (e.g. D&C), alcohol use and smoking	Education: —	-Women's ages ranged from 29 to 91 years
Dharmalingam et al, 2000[119]	•Cross-sectional •NA •Women aged 20 to 59 years in 1995 •New Zealand •1936 - 1975 •2,367 •252	Education; Occupational class	All self-reported hysterectomies	Calendar period, age, place of residence, religion, ethnicity, parity, pregnancy loss, tubal sterilisation, use of contraceptive	Education: — Occupational class: —	-Insufficient control for confounders -Association between hysterectomy and occupational class not adjusted for education

				devices (OC or IUD), marital status		
Kennedy and Jones, 2000[149]	•Cross-sectional •NA •A random community sample of women aged 20 to 69 years from Teesside •UK •1929 - 1978 •2,238 •234	Own and partner's occupational class	All self-reported hysterectomies	Other outcome considered: Irritable bowel syndrome	Occupational class: No association	-Women who participated in this postal survey will have been different from those who did not
Marshall et al, 2000[81]	•Prospective cohort •Up to 52 years (from birth) •Women born in one week in March 1946 who are members of the MRC NSHD •UK •1946 •1,755 •369	Education; Own and partner's occupational class	All self-reported hysterectomies	Parity, obesity and prior sterilisation	Education: — Partner's occupational class: — Own occupational class: No association (These associations attenuated with age)	-No distinction between hysterectomies for different reasons
Marshall et al, 2000[80]	•Prospective cohort •Up to 52 years (from birth) •Women born in one week in March 1946 who are members of the MRC NSHD •UK •1946 •1,755 •369	Education; Own and partner's occupational class; Father's occupational class in childhood	All self-reported hysterectomies	Parity, obesity and prior sterilisation	Father's occupational class in childhood: — Education: — Partner's occupational class: — Own occupational class: No association (There were greater differentials in hysterectomy by adult SEP at younger ages)	-No distinction between hysterectomies for different reasons -Only one indicator of childhood SEP considered
Ong et al, 2000[151]	•Cross-sectional •NA •Women aged 50 to 65 years, attending breast screening •Ireland	Health insurance ownership	All self-reported hysterectomies	Age at menarche, age at first pregnancy, parity, OC use and smoking	Owning private health insurance was significantly associated with increased risk of hysterectomy	-Insufficient control for confounders

	•1933 - 1948 •17,735 •3,936					
Progetto 2000[126]	•Cross-sectional •NA •Women attending menopause clinics •Italy •1919 - 1959 •25,644 •4,727	Education	Self-reported hysterectomies for benign conditions with or without oophorectomy (validated against medical records)	BMI, age, parity, whether an oophorectomy was also carried out, HRT use	Education: — (This association was maintained in multivariable analyses controlling for age, BMI and parity)	-Study population not representative of a general population - they are women who had referred themselves for treatment
Materia et al, 2002[150]	•Linkage study •NA •Women aged ≥35 years who underwent a hysterectomy in Rome, in 1997 •Italy •Not known (age range not reported) •Unknown – estimated from census data •3,141	Area based index of socioeconomic status	Hysterectomies separated by malignant or non-malignant cause		Area level of SES: — (overall) (This inverse association was only significant for hysterectomies for non-malignant causes in women aged 35-49 years, not in older women).	-Exposure status assigned at the group level -Denominator is an estimate and may have included women who had had hysterectomies in previous years
van der Vaart et al, 2002[140]	•Cross-sectional •NA •Random sample of women aged 35 to 70 years listed on a population register in a suburban area •Netherlands •1929 - 1964 •1,626 •209	Education	Self-reported hysterectomies	Age, parity, assisted delivery, incontinence	Education: —	-No control for confounders -Education coded as a binary variable -All information was self-reported
Hautaniemi and Sievert, 2003[141]	•Cross-sectional •NA • Mexican-American women living in the SW US enrolled in the Hispanic Health and Nutrition Examination Survey (HHANES), aged 20 to 74 years at baseline (1982-84) •USA •1908 - 1964	Education; Poverty	Self-reported hysterectomies	Age, language preference, parity, generation (2nd or 3rd generation in the US), marital status, tubal ligation, insurance, medicaid	Education: + Poverty: Lower levels of poverty were associated with increased risk of hysterectomy	-This study is not generalisable to a wider population -No information on numbers of women included is presented

	•Not presented •Not presented					
Hsia et al, 2003[142]	•Cross-sectional •NA •Participants in the Women's Health Initiative •USA •Not known (age range not reported) •1,501 •1,137	Education	Hysterectomies with or without oophorectomy	Ethnicity, region of US, family history of coronary disease, HRT use, alcohol use, exercise, diet, BMI, cardiovascular risk factors	Education: —	-No control for confounders
Westert et al, 2003[146]	•Linkage study •NA •Women > 25 years recorded as having had a hysterectomy in the Dutch hospital discharges for 1999 •The Netherlands •Not known (age range not reported) •Unknown – estimated from population estimates for 1999 •16,136	Average family income in post code area of residence	All recorded hysterectomies	Age, degree of urbanisation, province of residence	Income: —	-Exposure status assigned at the group level -Denominator is an estimate and may have included women who had had hysterectomies in previous years
Gardella et al, 2005[143]	•Cross-sectional •NA •Women who attended a veteran affairs medical centre between 1996 and 1998 •USA •1904 - 1976 •1,122 •359	Education	Self-reported hysterectomies	Age, race, parity, marital status, health symptoms	Education: No association	-Analyses only controlled for age -Study population is not representative of a general population
Howard et al, 2005[129]	•Cross-sectional (baseline data from prospective cohort study) •NA •Postmenopausal women aged 50 to 79 years recruited between 1994 and 1998 to participate in the Women's Health Initiative Observational study •USA	Education; Income	Hysterectomies self-reported at baseline assessment - a distinction was made between those with and without a bilateral	Main study was of the effect of hysterectomy status on cardiovascular risk factors but at baseline the associations	Education: — Income: —	-No control for confounders -Wide age range of study participants

	•1915 - 1948 •89,914 •36,938		oophorectomy (women who reported a bilateral oophorectomy only were excluded)	between hysterectomy and: SEP, marital status, exercise, age, age at first birth, age at menarche, parity, HRT use, smoking, hypertension, waist circumference and BMI were considered		
Zhang et al, 2005[130]	•Cross-sectional (baseline data from a cohort study) •NA •Women aged 45 to 74 years recruited between 1989 and 1992 from 13 American Indian communities to participate in the Strong Heart study •USA •1915 - 1947 •2,689 •820	Education	Self-reported hysterectomies with or without oophorectomy	Main study was of the effect of hysterectomy status on cardiovascular risk factors but at baseline the associations between hysterectomy and: age, years lived in Indian reservation, BMI, marital status, parity, fetal loss, oral contraceptive use, speaking native language, traditional medicine use and study centre were considered	Education: + (This association was maintained after adjustment for a range of potential confounders)	-Not generalisable to a national population
Ceausu et al, 2006[144]	•Cross-sectional •NA •All women aged 50-60 listed on a popular register as living in the Lund area in 1995	Education; Employment status	Self-reported hysterectomies	Use of medical care, reproductive characteristics, psychological and somatic symptoms,	Education: — Employment status: being employed was associated with lower odds of hysterectomy than	-Insufficient control for confounders -All information self-reported -No distinction between hysterectomies for different

•Sweden •1935 - 1945 •6,917 •800	HRT use, cardiovascular risk factors, BMI	unemployment	reasons

Appendix 3: Unadjusted survival analyses of the associations between indicators of SEP in childhood and hysterectomy by reason for hysterectomy in the NSHD

Indicator of SEP	Reason for hysterectomy (Hazard Ratio for hysterectomy for specified reason (95% CI)) [No. of hysterectomies]					
	Fibroids	**Menstrual disorders**	**Prolapse**	**Cancer**	**Other**	**Unknown**
Father's occupational class (N=1689)	[N=115]	[N=105]	[N=36]	[N=26]	[N=57]	[N=33]
I or II	1.00	1.00	1.00	1.00	1.00	1.00
IIINM	1.48 (0.86, 2.54)	1.86 (0.93, 3.72)	1.01 (0.37, 2.78)	11.47 (1.41, 93.20)	0.90 (0.33, 2.43)	0.62 (0.16, 2.34)
IIIM	1.09 (0.66, 1.78)	2.23 (1.23, 4.03)	1.05 (0.46, 2.44)	7.59 (0.96, 60.04)	1.38 (0.65, 2.92)	1.38 (0.57, 3.33)
IV or V	1.01 (0.59, 1.73)	2.35 (1.28, 4.32)	0.91 (0.36, 2.31)	9.71 (1.23, 76.64)	2.16 (1.05, 4.46)	1.23 (0.48, 3.20)
p-value	*0.49*	*0.02*	*0.99*	*0.01*	*0.09*	*0.57*
Maternal education (N=1595)	[N=107]	[N=100]	[N=34]	[N=26]	[N=49]	[N=30]
1 (High)	1.00	1.00	1.00	-	1.00	1.00
2	1.17 (0.53, 2.60)	2.32 (0.79, 6.78)	1.76 (0.29, 10.55)	1.00*	2.04 (0.60, 6.96)	1.56 (0.35, 6.97)
3	1.40 (0.67, 2.90)	2.74 (1.00, 7.54)	2.84 (0.57, 14.08)	8.58 (1.00, 73.44)	1.16 (0.31, 4.30)	1.24 (0.28, 5.56)
4 (Low)	1.14 (0.62, 2.12)	2.89 (1.17. 7.17)	2.48 (0.58, 10.53)	7.75 (1.04, 57.72)	1.73 (0.61, 4.88)	1.34 (0.40, 4.52)
p-value	*0.83*	*0.06*	*0.48*	*0.02*	*0.53*	*0.95*
Housing (N=1763)	[N=122]	[N=114]	[N=38]	[N=26]	[N=58]	[N=34]
Owner-occupied	1.00	1.00	1.00	1.00	1.00	1.00
Not owner-occupied	1.23 (0.84, 1.80)	1.14 (0.77, 1.69)	1.23 (0.62, 2.44)	1.05 (0.47, 2.35)	1.34 (0.76, 2.35)	1.81 (0.82, 3.99)
p-value	*0.29*	*0.50*	*0.55*	*0.91*	*0.31*	*0.12*
Shared a bedroom (N=1570)	[N=110]	[N=94]	[N=35]	[N=25]	[N=52]	[N=28]
No	1.00	1.00	1.00	1.00	1.00	1.00
Yes	1.00 (0.69, 1.45)	1.17 (0.78, 1.76)	1.47 (0.75, 2.90)	1.69 (0.75, 3.83)	1.31 (0.76, 2.27)	0.97 (0.46, 2.03)
p-value	*0.99*	*0.45*	*0.26*	*0.20*	*0.33*	*0.93*

Maternal education: 1 = Secondary and further or higher education ; 2 = Secondary only or Primary and further or higher education ; 3 = Primary and further education (no qualifications) ; 4 = Primary education only

* No hysterectomies in baseline group so top two categories combined

Appendix 4: Socio-economic position across the life course and hysterectomy in three British cohorts: a cross-cohort comparative study. BJOG: an International Journal of Obstetrics and Gynaecology 2005;112:1126-1133

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Socio-economic position across the life course and hysterectomy in three British cohorts: a cross-cohort comparative study

Rachel Cooper,[a] Debbie A. Lawlor,[b] Rebecca Hardy,[a] Shah Ebrahim,[b] David A. Leon,[c] Michael E.J. Wadsworth,[a] Diana Kuh[a]

Objective To examine the association between indicators of lifetime socio-economic position and rates of hysterectomy in three British cohorts.

Design Cross-cohort comparative study.

Setting Two cohorts: England, Scotland and Wales. Third cohort: Aberdeen, Scotland.

Population Three thousand two hundred and eight women born between 1919 and 1940, participating in the British Women's Heart and Health Study (BWHHS); 1394 women from the MRC National Survey of Health and Development (NSHD), followed up since birth in 1946; 3208 women born between 1950 and 1955, participating in the Aberdeen Children of the 1950s study, all with complete information on lifetime socio-economic position and hysterectomy status.

Methods Relative indices of inequality were derived for markers of socio-economic position in childhood and adulthood. Cox's regression models were used to test the association between these markers and hysterectomy.

Main outcome measure Self-reported hysterectomy with or without oophorectomy.

Results Adverse socio-economic position in childhood and as indicated by educational status was associated with reduced rates of hysterectomy in the oldest of the three cohorts (BWHHS), whereas conversely in the NSHD and Aberdeen cohorts it was associated with increased rates of hysterectomy. The unadjusted hazards ratios for hysterectomy comparing worst to best socio-economic position for father's social class were 0.73 (0.56, 0.96) for women from the BWHHS, 1.77 (1.19, 2.65) for those from the NSHD and 2.06 (1.46, 2.89) for those from the Aberdeen cohort. Associations between markers of adult socio-economic position and hysterectomy tended to be weaker in all three cohorts and often did not reach conventional levels of statistical significance.

Conclusions Our results show that hysterectomy rates are influenced by childhood socio-economic position and educational attainment, but that the nature of this association varies across these three British cohorts born in different decades of the 20th century. That there were no consistent or strong associations between adult SEP and hysterectomy rates suggest that social factors influencing rates of hysterectomy are likely to be those experienced or which develop in early life rather than those which develop later.

INTRODUCTION

Approximately 20% of women in the UK undergo hysterectomy by age 60 years[1,2] and this commonly performed procedure is usually discretionary.[2]

Biological and social factors acting at different stages of the life course[3,4] may increase the likelihood of hysterectomy. Indicators of adverse socio-economic position (SEP) in adulthood have often been found to be associated with increased risk of hysterectomy.[5–14] Education has been found to be inversely related to hysterectomy with more consistency between studies than other SEP variables.[5–9,12–15] Education may influence risk of hysterectomy through its impact on health choices, adult circumstances and behaviours,[16] but also because it is a marker of social conditions in earlier life.[17,18] Other factors influencing risk of hysterectomy, including obesity,[19] are associated with childhood socio-economic disadvantage.[20] There are conflicting findings about whether SEP in early life affects the risk of hysterectomy.[9,11] The influence of social factors may vary by geographic location and by birth cohort and be driven by differences in medical attitudes, culture or disease risk between places and over time,[21] but investigators rarely have the opportunity to examine this within one study.

We aimed to examine associations of child and adult SEP with hysterectomy rates in three British cohorts, of women born in the 1920s and 1930s [British Women's Heart and Health Study (BWHHS)], in 1946 [MRC National

[a]*MRC National Survey of Health and Development, Department of Epidemiology and Public Health, University College London, UK*
[b]*Department of Social Medicine, University of Bristol, UK*
[c]*Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, UK*

Correspondence: Ms R. Cooper, Department of Epidemiology and Public Health, University College London, 1-19 Torrington Place, London WC1E 6BT, UK.

Appendix 5: Summary of studies which have examined the relationship between body weight/composition and hysterectomy (listed in chronological order)

Reference	Study details: Study design Length of follow-up Study population Country of study N Number of hysterectomies	Direction of association considered	Definition of hysterectomy used	Measure/s of weight used	Other variables considered	Main findings (Direction of association with hysterectomy: + positive; — negative/inverse; No association)	Study limitations
Hjortland et al, 1976[155]	•Prospective cohort •Up to 18 years (9 biennial examinations) •Women aged 40 to 51 years who were pre-menopausal at the initial Framingham examination •USA •1,686 •297	Both	Hysterectomies with no oophorectomy or with unilateral oophorectomy (n=114); Hysterectomies with bilateral oophorectomy (n=183)	Relative weight (ratio of own body weight to smoothed median weight for a person in that sex and height group x 100) measured at biennial examinations	Effect of menopausal status on: blood pressure, serum cholesterol, blood glucose, vital capacity and haemoglobin was also investigated	Relative weight: + (but only when comparing women who had a hysterectomy with bilateral oophorectomy with their controls. Differences in weight were only statistically significant at the pre-menopausal exam. Difference in weight between women who had hysterectomy without bilateral oophorectomy and their controls not significant).	-Control group remained pre-menopausal -No control for confounders
Koepsell et al, 1980[122]	•Cross-sectional •NA •Women aged 35 to 74 years in 2 urban Washington counties during 1976-77 •USA •1,087 •358	None proposed	All self-reported hysterectomies	Self-reported BMI (height and weight) at time of the study	Age, race, marital status, parity, age at first birth, ever had a miscarriage or caesarean, regular menses, other health conditions and practices, income, education	BMI: No association	-All data self-reported -Data measured at one time point -Wide age range of study participants -BMI measured after hysterectomy so cannot establish direction of

							association
Meilahn et al, 1989[125]	•Cross-sectional •NA •Women aged 40 to 52 years selected at random from a list of women holding driver's licenses in Pittsburgh, Pennsylvania in 1983 •USA •2,137 •583	None proposed	Self-reported hysterectomies with or without concomitant oophorectomy or oophorectomy alone for any reason	Self-reported BMI (height and weight) at time of the study (phone interview)	Current age, age at menarche, age at first birth, race, marital status, parity, education, cigarette smoking, alcohol consumption and current religion	BMI: + (This association was not statistically significant in multivariable models)	-All data self-reported -Validity of BMI measure not examined -BMI measured after hysterectomy so cannot establish direction of association -No distinction made between oophorectomy and hysterectomy
MacLennan et al, 1993[124]	•Cross-sectional •NA •Women aged ≥40 years interviewed as part of the South Australian Health Omnibus Survey in October 1991 •Australia •1,047 •292	None proposed	All self-reported hysterectomies	Self-reported BMI at time of the study (personal interview)	Age, country of birth, income, educational level, smoking status, alcohol consumption, diabetes, blood pressure, HRT use, mammography attendance and frequency of GP visits	BMI: +	-No control for confounders -BMI measure provided after hysterectomy so cannot establish direction of association -Categorisation of BMI oversimplified (normal weight vs. overweight or obese)
Luoto et al, 1995[156]	•Cross-sectional •NA •Women aged 30 to 95 years between 1977 and 1980 from 40 regions •Finland •3,780 •218	None proposed	Self-reported hysterectomies separated into 2 groups: those with ovarian preservation (n=163) and those with bilateral oophorectomy (n=55)	BMI (height and weight) measured during a health examination	Other outcomes: glucose, cholesterol, HDL cholesterol and triglyceride levels, use of alcohol, systolic and diastolic blood pressure	BMI: + (This association was maintained after adjustment for age)	-Women excluded if reports could not be verified which could have introduced bias -Wide age range of women -Insufficient control for confounders -No consideration

							of pre-hysterectomy BMI so cannot establish direction of association
Ravn et al, 1995[157]	•Cross-sectional •NA •Women aged 50 to 59 years who had pre-menopausal hysterectomy or were naturally menopausal who responded to a questionnaire in 1992 •Denmark •496 •69	None proposed	Self-reported pre-menopausal hysterectomies with preservation of at least one ovary	Weight and total, leg, arm and trunk fat measured during a health examination	Other variables: height, bone mineral density, hormone levels	Weight: + Levels of body fat: + (Of the associations with levels of body fat only the association with levels of arm fat was significant)	-No control for confounders -No adjustment for height -Cannot establish temporal nature of association
Akahoshi et al, 1996[202]	•Prospective cohort •Up to 30 years (biennial examinations between 1958-9 and 1988-9) •Women aged < 53 years in 1958, who had not experienced menopause by 1955 but had experienced surgical or natural menopause by 1989 and age matched male controls •Japan •1,501 •134	Effect of hysterectomy on weight	Any reported hysterectomies	BMI (height and weight) measured at biennial examinations	Other outcomes: cholesterol, systolic blood pressure Other explanatory variables considered: natural menopause	BMI: No association	-Comparison group was men -No control for confounders
Hann and Asghar, 1996[158]	•Cross-sectional •NA •Women who participated in the Behavioural Risk Factor Surveillance System telephone survey in Oklahoma between 1991 and 1994 •USA •Not reported •Not reported	None proposed	Not reported	BMI (height and weight) reported during telephone survey	The association between obesity and: gender, race, education, smoking status, hypertension, age, diabetes, diet and lifestyle was examined	No association was found between 'severe' obesity and hysterectomy. Women who had had a hysterectomy had a higher prevalence of 'moderate' obesity.	-BMI reported after hysterectomy so cannot establish direction of association -Not clear whether there was any control for confounders
Settnes et al, 1996[154] (Prevalence	•Cross-sectional •NA •Women aged 30, 40, 50 or 60 years	Effect of weight on hysterectomy	Self-reported hysterectomies for benign diseases	BMI (weight and height) measured at initial examination;	Age, smoking habits, alcohol consumption,	Unstable weight: + (fluctuations in weight associated with increased	-Current BMI was measured after hysterectomy

study)	selected at random in 1982 •Denmark •1,765 •183		(n=155) (pre-malignant and malignant cases excluded (n=28))	self-reported BMI at age 25 years; stability of weight (self-reported fluctuations in weight of more than 5kg except during pregnancy); having ever lost > 5kg by slimming diet or diet pills; overweight relatives	plasma lipid levels and psychosomatic and neurotic symptoms	risk of hysterectomy) Slimming diets: + (having been on a diet increased risk of hysterectomy) (These associations were maintained after adjustment for potential confounders)	-Reliant on retrospective recall of weights in earlier life -Validity of BMI measures not examined -Other potential confounders not considered
Settnes et al, 1996[154] (Incidence study)	•Prospective cohort •Up to 8 years (1982 to 1990) •Women from the above prevalence study without prior hysterectomy •Denmark •1,582 •57	Effect of weight on hysterectomy	Hysterectomies for benign diseases (n=42) (pre-malignant and malignant cases excluded (n=15)) reported by the National Patient Register	As for prevalence study above	As for prevalence study above	All measures of weight: + (Unstable weight retained significance after adjustment for confounders)	-Small number of hysterectomies -Retrospective, self-reported weight measures used
Sowers et al, 1996[203]	•Prospective cohort •4.5 years •White women age 20 to 40 years who were menstruating at baseline •USA •404 •40	Effect of hysterectomy on weight (but results tables allow consideration of both)	Hysterectomies (without attendant oophorectomy) (n=16) or oophorectomy (n=24)	Body weight, waist to hip ratio, BMI, % body fat and fat and lean body mass measured using standardised procedures by anthrompometrists	Menstrual status, lifestyle, reproductive history and hormone status	Fat mass: + (Women who had had an oophorectomy had more pronounced increases in fat mass compared to women with hysterectomy or women still menstruating).	-Small number of women who had had an oophorectomy or hysterectomy -The difference in weight pre-procedure was not formally tested
Carranza-Lira et al, 1997[204]	•Case control •NA •Women who had undergone a hysterectomy previously and were attending a clinic for climacteric problems and a group without hysterectomy also attending the	Effect of hysterectomy on weight	'Simple' hysterectomies	BMI (height and weight) measured at clinic	Other outcomes: depression; libido reduction; FSH, estradiol and total cholesterol levels	BMI: No association (after adjustment for age and time since hysterectomy)	-Difficult to establish how selection of controls was made -No clear definition of hysterectomy -No control for pre-

	clinic for similar problems •Mexico •570 •285						hysterectomy BMI
Kritz-Silverstein et al, 1997[159]	•Cross-sectional •NA •Women aged 50 to 89 years between 1984 and 1987 who were participating in the Rancho-Bernardo study •USA •1,150 •505	None proposed	Hysterectomies with or without oophorectomy	Self-reported BMI (height and weight) and waist:hip ratio	Study examined effect of hysterectomy on heart disease risk factors	BMI: No association Waist:hip ratio: No association	-No control for confounders -Cross-sectional analysis so direction of association cannot be established
Stoney et al, 1997[205]	•Prospective cohort •3 months (women measured prior to operation and then 3 months after) •Middle-aged pre-menopausal women who were to undergo either a total abdominal hysterectomy (TAH) or a bilateral salpingo oophorectomy (BSO) •USA •29 •19	Effect of hysterectomy on weight	Total abdominal hysterectomies (n=19)	BMI (height and weight), body fat and waist:hip ratio measured at clinic visits	Changes in other variables tested: hormone levels, blood pressure, heart rate, total cholesterol, HDL, LDL and triglyceride levels	Pre-operatively women who were to have BSO had higher BMI than women who were to have a TAH. By 3 months post surgery there were no differences in measures of body composition by type of surgery.	-Small sample size -No adjustment for confounders -No 'healthy' comparison group -No analysis of change within women in the same group over time -Short length of follow-up
Brown et al, 1998[160]	•Cross-sectional •NA •Women aged 45 to 49 years who participated in the baseline survey for the Australian Longitudinal Study on Women's Health •Australia •13,431 •3,040	None proposed	Any self-reported hysterectomies	Self-reported BMI (height and weight) at time of the study (postal questionnaire)	Other outcomes: hypertension, diabetes, other surgical procedures, back pain, chronic tiredness and health care use. Factors adjusted for: area of residence, education, smoking and exercise	BMI: +	-Self-reported hysterectomy, height and weight measurements -High level of non-response -BMI reported after hysterectomy so cannot establish direction of association

Harlow and Barbieri, 1999[120]	•Cross-sectional •NA •Women aged 36 to 44 years listed in the Massachusetts Town Books and not naturally post menopausal at the time of the study •USA •4,278 •114	Effect of weight on hysterectomy	All self-reported hysterectomies	Self-reported BMI (height and weight) at time of the study	Age, race, marital status, smoking habits, age at menarche, history of irregular cycles, parity, OC use, history of period pain, endometriosis or uterine fibroids, removal of an ovary, education	BMI: +	-Self-reported hysterectomy, height and weight measurements -BMI reported after hysterectomy so cannot establish direction of association
Kirchengast et al, 2000[161]	•Retrospective cohort •NA •Viennese women aged between 47 and 57 years who had had a hysterectomy or had undergone natural menopause •Austria •184 •54	Both	Hysterectomies using the abdominal route for a non-malignant purpose with at least one ovary conserved	Self-reported retrospective recall of pre-menopausal weight or clinical recollection of weight status pre-hysterectomy ; body composition (abdominal fat mass; fat percentage; fat distribution) post hysterectomy or menopause		Mean body weight prior to hysterectomy/ menopause: + (but this was not significant). Mean body weight and fat tissue (especially in the abdominal region) post procedure/ menopause: +	-Pre-menopausal weight was measured differently from pre-hysterectomy weight -Pre-menopausal weight retrospectively recalled -Only basic statistical analyses were conducted and no potential confounders were controlled for -Body composition was only measured post- procedure/ menopause
Progetto Menopausa Italia Study Group, 2000[126]	•Cross-sectional •NA •Women attending menopause clinics having referred themselves •Italy •25,644	Effect of weight on hysterectomy	Self-reported hysterectomies for benign conditions with or without oophorectomy (checked with	BMI (height and weight) measured during clinic visit	Education, age, parity, whether an oophorectomy was also carried out, HRT use	BMI: + (This association was maintained after adjustment for age, education and parity)	-Study population not representative of a general population -High percentage of missing values for

	•4,727		medical records)				BMI -BMI was measured after hysterectomy so the direction of association cannot be established
Matthews et al, 2001[206]	•Cross-sectional •NA •Women aged 40 to 55 years living in any one of the seven regions selected from the SWAN study •USA •14,148 •2,924	Effect of hysterectomy on weight	Hysterectomies or bilateral oophorectomies	BMI (height and weight) as reported to phone interviewer	Explanatory variables: physical inactivity, postmenopausal hormone use, ethnicity and age	BMI: + (This association was maintained after adjustment for all covariates including age),	-No distinction between bilateral oophorectomy and hysterectomy made -Cannot examine temporal relationship -Weight and height self-reported
Hsia et al, 2003[142]	•Cross-sectional •NA •Participants in the Women's Health Initiative •USA •1,501 •1,137	None proposed	Hysterectomies with or without oophorectomy	Self-reported BMI at baseline assessment	Ethnicity, region of US, family history of coronary disease, HRT use, alcohol use, exercise, diet, educational level, cardiovascular risk factors	BMI: +	-No control for confounders -Cannot examine temporal relationship
Lambert et al, 2003[207]	•Cross-sectional •NA •Women aged 35 to 79 years who participated in the Busselton Health Study in 1994/5 and women aged 35 to 69 years from Perth who were controls in the 1994 National Heart Foundation Risk Factor Survey •Australia •2,540 •646	Effect of hysterectomy on weight	Self-reported hysterectomies	BMI (height and weight) and waist:hip ratio measured at the time of the surveys	Main outcome: HRT use Other variables considered: marital status, place of birth, occupation, physical activity levels, alcohol consumption, smoking status, blood pressure, cholesterol,	BMI: + Waist:hip ratio: + (Women who had had a hysterectomy and were not using HRT had the highest BMI and waist:hip ratio even after adjustment for age and place of residence).	-Cannot examine temporal relationship

					triglycerides		
Bastian et al, 2005[208]	•Cross-sectional •NA •Women aged 60 to 102 years participating in The Cache County Study on Memory, Health, and Aging •USA •2,035 •Not reported	Effect of hysterectomy on weight	Hysterectomies, oophorectomies or both	Self-reported BMI (height and weight) at baseline assessment	Main predictor of interest: Parity Other variables considered: education, work history, marital status, age at menarche, age at menopause, use of HRT, use of oral contraceptives, breast-feeding, physical activity, ever smoked, alcohol consumption	BMI: No association	-BMI categorised into only 2 groups (obese vs not obese) -Height and weight self-reported
Farquhar et al, 2005[153]	•Cross-sectional (analysis of baseline data from a cohort study) •NA •Women aged <46 years who were recruited from gynaecological surgical bookings or local newspaper adverts •New Zealand •516 •257	None proposed	Hysterectomies with or without unilateral oophorectomy performed for reasons other than gynaecological malignancy identified from a range of hospitals' surgical bookings	BMI measured in the week before surgery	Investigators studied differences in age, ethnicity, smoking, parity and BMI between the hysterectomy and comparison group at baseline	BMI: +	-No control for confounders -Unclear how BMI was measured and whether similar methods were used for both the hysterectomy and comparison group
Grimm et al, 2005[162]	•Cross-sectional •NA •Caucasian women seeking counseling for various reasons in Germany or Austria between May 2001 and June 2002 •Austria and Germany •1058 •192	Effect of weight on hysterectomy	Pre-menopausal hysterectomies	BMI	Study of the effect of a genetic polymorphism on female reproductive characteristics	BMI: + (This was maintained after adjustment for age and time since menopause. The effect was modified by the vitamin D receptor gene polymorphism – women	-Cannot examine temporal relationship -Not clear from methods whether BMI used was a pre-hysterectomy measure and whether it was self-

						with BMI >25 and no mutant VDR alleles had higher odds of pre-menopausal hysterectomy than women with BMI >25 and at least one mutant VDR allele).	reported or measured by doctors -BMI categorised into only 2 groups
Howard et al, 2005[129]	•Cross-sectional (baseline data from prospective cohort study) •NA •Postmenopausal women aged 50 to 79 years recruited between 1994 and 1998 to participate in the Women's Health Initiative Observational study •USA •89,914 •36,938	None proposed	Hysterectomies self-reported at baseline assessment - a distinction was made between those with and those without a bilateral oophorectomy (women who reported a bilateral oophorectomy only were excluded)	BMI (height and weight) and waist circumference measured during baseline assessment	At baseline the associations between hysterectomy and: marital status, exercise, age, age at first birth, age at menarche, parity, HRT use, smoking, hypertension, income and educational level were considered	BMI: + Waist circumference: +	-Cannot examine temporal relationship -Analyses of difference in BMI and waist circumference by hysterectomy status were all unadjusted
Kuh et al, 2005[163]	•Prospective cohort •53 years •Female participants of the MRC NSHD •UK •1,303 •104	None proposed	Self-reported hysterectomies, not using hormone replacement therapy	BMI (height and weight), waist circumference and waist:hip ratio measured by nurses at age 43 and 53 years	Adjustments made for childhood and adult SEP and smoking status	BMI at age 53: + Waist circumference at age 53: + (These associations attenuated after adjustment for confounders and BMI/waist circumferences at age 43 years).	
Tempfer et al, 2005[164]	•Cross-sectional •NA •White women of Austrian and German origin seeking advice on	Effect of weight on hysterectomy	Pre-menopausal hysterectomies	BMI at time of hysterectomy self-reported in retrospective	No adjustment made for potential confounders.	BMI: +	-Retrospective self-reports of height and weight -BMI only

	HRT between March 2001 and December 2003 •Austria and Germany •728 •104			questionnaire			categorised into 2 groups -Not clear how representative the study population was or who the comparison group were -No adjustment made for potential confounders -Cannot examine temporal relationship
Zhang et al, 2005[130]	•Cross-sectional (baseline data from a cohort study) •NA •Women aged 45 to 74 years recruited between 1989 and 1992 from 13 American Indian communities to participate in the Strong Heart study •USA •2,689 •820	None proposed	Self-reported hysterectomies with or without oophorectomy	BMI at time of baseline study	At baseline the associations between hysterectomy and: age, years lived in Indian reservation, educational level, marital status, parity, fetal loss, oral contraceptive use, speaking native language, traditional medicine use and study centre were considered	BMI: No association	-Cannot examine temporal relationship -Study population not representative of a general population so results not generalisable
Ceausu et al, 2006[144]	•Cross-sectional •NA •All women aged 50-60 listed on a popular register as living in the Lund area in 1995 •Sweden •6,917	Effect of weight on hysterectomy	Self-reported hysterectomies	Weight at age 25 years retrospectively recalled, increases in body weight of more than 5kg in the 5 years up to the study; current	Use of medical care, symptoms, HRT use, cardiovascular risk factors, reproductive characteristics,	Weight at age 25 years: + Increases in body weight of > 5kg in the last 5 years: + Current waist:hip ratio: No association Results for BMI not	-Weight at age 25 years not adjusted for height -Weight in earlier life was retrospectively recalled

	•800			waist:hip ratio and BMI measured at laboratory examination	educational level, employment status	reported.	-Insufficient control for confounders
Hefler et al, 2006[165]	•Cross-sectional •NA •Women seeking counselling, mainly for post-menopausal disorders or risk assessment for malignancies •Germany and Austria •1,345 •317	Effect of weight on hysterectomy	Self-reported hysterectomies	Weight and size at time of menopause/surgery retrospectively recalled	Parity, age at first birth, smoking status	BMI: + (This was maintained after adjustment for reproductive factors and smoking)	-Weight retrospectively reported -Not possible to establish a clear temporal relationship between weight and hysterectomy -Study population not representative of a general population

Appendix 6: Summary of studies which have examined the association between reproductive characteristics and hysterectomy (listed in chronological order)

Reference	Study details: Study design Length of follow-up Study population Country of study N Number of hysterectomies	Reproductive characteristics	Definition of hysterectomy used	Other variables considered	Main findings (Direction of association with hysterectomy: + positive; — negative/inverse; No association)	Study limitations
Koepsell et al, 1980[122]	•Cross-sectional •NA •Women aged 35 to 74 years in 2 urban Washington counties during 1976-77 •USA •1,087 •358	Parity; Age at first birth; Ever had miscarriage	All self-reported hysterectomies	Age, race, marital status, education, income, ever had a caesarean, regular menses, other health conditions	Parity: non-linear (women who were nulliparous had a higher risk of hysterectomy than women with 1 child but lower risk than women with >1 child. This effect was attenuated after adjustment for age at first birth). Age at first birth: — (This was independent of income and parity). Ever had a miscarriage: + (i.e. associated with increased risk of hysterectomy).	-All measures were self-reported
Meilahn et al, 1989[125]	•Cross-sectional •NA •Women aged 40 to 52 years selected at random from a list of women holding driver's licenses in Pittsburgh, Pennsylvania, in 1983 •USA •2,137 •583	Age at menarche; Age at first birth; Parity	Self-reported hysterectomies with or without concomitant oophorectomy or oophorectomy alone for any reason	Current age, education, race, marital status, cigarette smoking, alcohol consumption, BMI and current religion	Age at menarche: — Age at first birth: — Parity: Nulliparity was associated with increased risk of hysterectomy among black women.	-All measures were self-reported -Age at menarche was categorised into only 2 groups -No distinction made between oophorectomy and hysterectomy
Luoto et al, 1992[123]	•Cross-sectional •NA	Parity	Self-reported hysterectomies	Education, occupation, age	Parity: —	-Insufficient control for potential confounders

	•Women aged 45 to 64 years old randomly selected from a population census •Finland •1713 (86% of those selected) •329					
Santow and Bracher, 1992[127]	•Cross-sectional •NA •Women aged 20 to 59 years •Australia •2,547 •248	Parity; Spontaneous fetal losses (i.e. miscarriage); Oral contraceptive and intrauterine device use; Tubal sterilisation	All self-reported hysterectomies	Age, marital status, contraceptive failure, religion, place and region of residence, calendar period	Parity: + (risk increased after the third birth and was greater if the third child was born before age 25) Experience of two or more fetal losses: + (but only before age 35) Oral contraceptive use for over 5 years: — (i.e. reduced risk) IUD use: no association Tubal sterilisation: — (i.e. reduced risk)	-Level of adjustment for confounders unclear
Vessey et al, 1992[1]	•Prospective cohort •Up to 21 years •Women in the Oxford Family Planning Association study who were aged 25 to 39 years, married, white and British and a current user of contraception at time of enrollment •UK (England and Scotland) •17,032 •1,885	Parity	All recorded hysterectomies	Age, calendar period, husband's social class	Parity: + (when considering hysterectomies for all reasons combined) (Nulliparous women had significantly higher rates of hysterectomy for fibroids but significantly lower rates of hysterectomy for menstrual problems and prolapse than parous women There was no significant association between parity and hysterectomies for endometriosis or pre-cancer/cancer. These effects were not explained by calendar period,	-Women in this cohort were not representative as they must have been attending a family planning clinic and consented to take part in the study

					age or husband's occupational class).	
Parazzini et al, 1993[171]	•Cross-sectional •NA •Women acting as controls in a case-control study of breast cancer in Milan •Italy •2,916 •355	Parity	Unknown	Education, menopausal status, cohort of birth	Parity: No association	
Dennerstein et al, 1994[132]	•Cross-sectional •NA •Random sample of Australian born Melbourne women aged 45 to 55 years •Australia •2,001 •420	Age at menarche	All self-reported hysterectomies (Women with a uni- or bi-lateral oophorectomy excluded)	Age, education, pre-menstrual symptoms, number of D&C procedures, number of non-gynaecological operations, use of HRT, smoking, use of prescription medicines	Age at menarche: —	-All measures were self-reported and the validity of these were not tested -Unclear how many potential confounders, if any, were adjusted for
Brett et al, 1997[137]	•Prospective cohort •Up to 20 years •Women enrolled in the NHANES I study who were 25 to 49 years old and had not had a hysterectomy at the time of their first examination (1971-75) •USA •4,601 (some of these women excluded) • 1,648	Age at first birth; Parity; Number of miscarriages	All self-reported hysterectomies which could be confirmed by hospital records (some analyses performed by reason: cancer, fibroids, uterine prolapse, menstrual disorders)	Education, residence in a poverty census enumeration district, race	Hysterectomies for all reasons combined: Age at first birth: — Parity: + 3 or more miscarriages: + (Women who had 3 or more miscarriages were at greater risk of hysterectomy for prolapse but lower risk of hysterectomy for fibroids compared with women with 0-2 miscarriages).	-A large proportion of hysterectomy cases were excluded -Unclear how valid the measures of reproductive characteristics were
Settnes et al, 1997[167] (Prevalence study)	•Cross-sectional •NA •Women aged 30, 40, 50 or 60 years selected at random in 1982	Age at menarche; Parity; Ever had an abortion (spontaneous or	Self-reported hysterectomies for benign diseases (n=155) (pre-	Age, education, social status, unstable weight, BMI, physical	Age at menarche: — Parity: non-linear (multi-parous ($\geq$4 births) and nulliparous women had higher	-Retrospective, self-reported measures used

	•Denmark •1,765 •183	induced); Oral contraceptive use	malignant and malignant cases excluded (n=28))	activity, pelvic inflammation	risk than women with 1-3 children) Abortions: No association Short-term use of OC (1-4 years): + Long term use of OC (≥5 years): — (After adjustment for social and weight-related factors the effect of age at menarche and OC use was still significant but the effect of multiparity was no longer significant)	
Settnes et al, 1997[167] (Incidence study)	•Prospective cohort •Up to 8 years (1982 to 1990) •Women from the above prevalence study without prior hysterectomy •Denmark •1,582 •57	Age at menarche; Parity; Ever had an abortion (spontaneous or induced); Oral contraceptive use	Hysterectomies for benign diseases (n=42) (pre-malignant and malignant cases excluded (n=15)) reported by the National Patient Register	Age, education, social status, unstable weight, BMI, physical activity, pelvic inflammation, breastfeeding	Age at menarche: — Parity: + Ever having had an abortion: + Short-term use of OC: + (Effects of having had an abortion and short-term OC use retained significance after adjustment for social and weight-related factors).	-Small number of hysterectomies so analyses have low power -Retrospective, self-reported measures used -No distinction made between spontaneous and induced abortions
Harlow and Barbieri, 1999[120]	•Cross-sectional •NA •Women aged 36 to 44 years listed in the Massachusetts Town Books between 1995 and 1997 and not naturally post menopausal at the time of the study •USA •4,278 •114	Age at menarche; Parity; Oral contraceptive use	All self-reported hysterectomies	Age, race, marital status, BMI, smoking habits, educational level, history of irregular cycles, history of period pain, endometriosis or uterine fibroids, removal of an ovary	Age at menarche: — Parity: No association Oral contraceptive use: No association	-Insufficient control for confounders -All information was self-reported retrospectively
Treloar et al, 1999[128]	•Cohort •Up to 14 years •Women enrolled in a nationwide	Parity; Problems conceiving	All self-reported hysterectomies	Age, education, medical consultation for	Parity: non-linear (low parity reduced the risk of hysterectomy whereas	-Women's ages ranged from 29 to 91 years -All information was self-

	cohort of female twin pairs •Australia •3,096 •524			pelvic pain, menstrual problems, history of endometriosis, PID or fibroids, previous investigations or interventions (e.g. D&C), alcohol use and smoking	nulliparity was associated with increased risk) Consulting a doctor about problems conceiving: + (i.e. increased risk of hysterectomy)	reported -Reasons for hysterectomy not considered despite this information being available -Analyses performed unclear
Dharmalingam et al, 2000[119]	•Cross-sectional •NA •Women aged 20 to 59 years in 1995 •New Zealand •2,367 •252	Parity; Fetal loss; Ever used oral contraceptives or intrauterine device; Prior tubal sterilisation	All self-reported hysterectomies	Calendar period, age, place of residence, religion, ethnicity, , marital status, educational level, occupation	Parity: + Fetal loss: + Oral contraceptive use: No association Tubal sterilisation: No association	-Insufficient control for confounders -All information was self-reported retrospectively
Ong et al, 2000[151]	•Cross-sectional •NA •Women aged 50 to 65 years, attending breast screening •Ireland •17,735 •3,936	Age at menarche; Age at first pregnancy; Parity; Oral contraceptive use	All self-reported hysterectomies	Health insurance ownership, smoking habits	Age at menarche: No association Age at first pregnancy: No association Parity: + Oral contraceptive use: +	-Insufficient control for confounders -All information was self-reported retrospectively
Progetto Menopausa Italia Study Group, 2000[126]	•Cross-sectional •NA •Women attending menopause clinics who had referred themselves for treatment •Italy •25,644 •4,727	Parity	Self-reported hysterectomies for benign conditions with or without oophorectomy (checked with medical records)	Education, age, BMI, whether an oophorectomy was also carried out, HRT use	Parity: No association	-Study population not representative of a general population
van der Vaart et al, 2002[140]	•Cross-sectional •NA •Random sample of women aged 35 to 70 years listed on a population register in a suburban area	Parity	Self-reported hysterectomies	Age, education, assisted delivery, incontinence	Parity: +	-No control for confounders -Parity coded as a binary variable -All information was self-reported

	•Netherlands •1,626 •209					
Hautaniemi and Sievert, 2003[141]	•Cross-sectional •NA • Mexican-American women living in the SW US enrolled in the Hispanic Health and Nutrition Examination Survey (HHANES), aged 20 to 74 years at baseline (1982-84) •USA •Not presented •Not presented	Parity; Prior tubal sterilisation	Self-reported hysterectomies	Age, language preference, generation (2nd or 3rd generation in the US), marital status, insurance, medicaid, education, poverty	Parity: + Prior tubal sterilisation: No association	-This study is not generalisable to a wider population -No information on numbers of women included was presented
Farquhar et al, 2005[153]	•Cross-sectional (analysis of baseline data from a cohort study) •NA •Women aged <46 years who were recruited from gynaecological surgical bookings or local newspaper adverts •New Zealand •516 •257	Parity	Hysterectomies with or without unilateral oophorectomy performed for reasons other than gynaecological malignancy identified from a range of hospitals' surgical bookings	Investigators studied differences in age, ethnicity, smoking, parity and BMI between the hysterectomy and comparison group at baseline	Parity: +	-No control for confounders
Gardella et al, 2005[143]	•Cross-sectional •NA •Women who attended a veteran affairs medical centre between 1996 and 1998 •USA •1,122 •359	Parity	Self-reported hysterectomies	Age, race, education, marital status, health symptoms	Parity: +	-Analyses only controlled for age -Study population is not representative of a general population
Howard et al, 2005[129]	•Cross-sectional (baseline data from prospective cohort study) •NA •Postmenopausal women aged 50 to 79 years recruited between	Age at menarche; Age at first birth; Parity	Hysterectomies self-reported at baseline assessment - a distinction was	At baseline the associations between hysterectomy and: reproductive	Age at menarche: — Age at first birth: — Parity: +	-No control for confounders

	1994 and 1998 to participate in the Women's Health Initiative Observational study •USA •89,914 •36,938		made between those with and those without a bilateral oophorectomy (women who reported a bilateral oophorectomy only were excluded)	characteristics, education, income, marital status, exercise, age, HRT use, smoking, hypertension, waist circumference and BMI were considered		
Zhang et al, 2005[130]	•Cross-sectional (baseline data from a cohort study) •NA •Women aged 45 to 74 years recruited between 1989 and 1992 from 13 American Indian communities to participate in the Strong Heart study •USA •2,689 •820	Parity; Oral contraceptive use; Fetal loss	Self-reported hysterectomies with or without oophorectomy	At baseline the associations between hysterectomy and: age, years lived in Indian reservation, education, BMI, marital status, speaking native language, traditional medicine use and study centre were considered	Parity: No association Oral contraceptive use: No association Experience of ≥3 fetal losses: +	-Study population not representative of a general population
Ceausu et al, 2006[144]	•Cross-sectional •NA •All women aged 50-60 listed on a popular register as living in the Lund area in 1995 •Sweden •6,917 •800	Parity; Age at first birth; Intervals between menstrual cycles; Amenorrhic episodes; Hormonal contraceptive use	Self-reported hysterectomies	Use of medical care, symptoms, HRT use, cardiovascular risk factors, BMI, educational level, employment status	Parity: No association Age at first birth: — Length of interval between menstrual cycles: — Frequency of amenorrhic episodes: — Hormonal contraceptive use: No association	-Insufficient control for confounders -All information self-reported
Hefler et al, 2006[165]	•Cross-sectional •NA •Women seeking counselling, mainly for post-menopausal disorders or risk assessment for malignancies	Parity; Age at first birth	Self-reported hysterectomies	BMI, smoking status	Parity: + Age at first birth: — (These associations were not independent of BMI and smoking)	-Study population not representative of a general population -All measures were self-reported

•Germany and Austria	•1,345	•317

Appendix 7: Summary of publications which have assessed the health consequences of hysterectomy in the NSHD

Reference	Details of consequence/s studied	Main exposure examined	Other factors considered	Relevant findings
Cardiovascular disease risk factors (including BMI)				
Kuh, Langenberg, Hardy et al, 2005[163]	Cardiovascular risk factors (BMI, glycosolated haemoglobin, blood pressure, high density lipoprotein, low density lipoprotein and total cholesterol) at age 53 years and changes in two of these factors (BMI and blood pressure) since age 43 years	Menopausal status at age 53 years (pre-menopausal, peri-menopausal, post-menopausal, hysterectomy, HRT user)	Potential confounders: history of smoking, adult and childhood SEP	In unadjusted analyses hysterectomised women were heavier, had the worst total and LDL cholesterol levels and relatively high glycosolated haemoglobin levels compared with women in other menopausal status groups. However, in multivariable analyses CVD risk factor levels of hysterectomised women differed little from those naturally menopausal women not on HRT. In analyses of BMI at age 53 years, adjustment for BMI at age 43 years attenuated the size of the association.
Health symptoms				
Kuh, Wadsworth and Hardy, 1997[416]	Symptoms reported at age 47 years (Psychological symptoms (anxiety and depression, tearfulness, irritability, panic attacks, forgetfulness); Somatic symptoms (pins and needles, dizziness, aches and pains, palpitations, skin crawling sensations, breast tenderness, severe frequent headaches, frequency of urine); Vasomotor symptoms (hot flushes, cold/night sweats, trouble sleeping); Sexual difficulties (difficulties with intercourse, vaginal dryness))	Menopausal status by age 47 years (pre-menopausal, peri-menopausal, post-menopausal, hysterectomy, HRT use, periods stopped for other reason)	Health (e.g. report of chronic health problems), smoking behaviour and educational attainment earlier in life, work and family stress	Hysterectomised women reported more of all the somatic symptoms than their peers in any other menopausal status group. They also reported more psychological symptoms than those women who were in other menopausal states although these symptoms were also reported by a similar proportion of HRT users. Hysterectomised women reported similar levels of vasomotor symptoms (hot flushes, cold/night sweats, trouble sleeping) to perimenopausal women and lower levels than postmenopausal women. The prevalence of sexual difficulties and trouble sleeping among hysterectomised women was similar to that among postmenopausal women. These associations were all maintained after adjustment for confounders
HRT use				
Kuh, Hardy and Wadsworth,	Timing of uptake of HRT use up to age 50 years	A number of potential social and behavioural	In multivariable models other predictors found to be	Women who had had a hysterectomy AND oophorectomy had rates for having tried HRT over 4 times higher than

2000[417]		influences including hysterectomy or oophorectomy by age 43 years	important were adjusted for.	women who had had neither operation. Women who had had a hysterectomy had double the rate of HRT uptake compared to women who had had neither operation.
Incontinence				
Kuh, Cardozo and Hardy, 1999[393]	Symptoms of incontinence as reported at age 48 years Type: Stress incontinence (losing urine when coughing, sneezing, laughing, running or exercising); Urge incontinence (ever having an urgent and strong desire to pass urine which is difficult to control) Severity: Severe (occurring twice a month or more over the past year and reported loss of more than a few drops of urine); Moderate (reported one but not both the above symptoms)	Childhood enuresis (defined by maternal reports of bedwetting or wetting during the day at age 6 years)	Parity; number of caesarean deliveries; BMI at age 43 years; history of kidney or bladder infections; menopausal status (including whether hysterectomised); self-perceived health; health care utilisation (no. of consultations with a Dr in past 12 months); education	Hysterectomised experienced increased odds of urge incontinence in unadjusted models (when compared to women who had not had a hysterectomy) but adjustment for childhood enuresis, urinary or kidney infections, BMI, symptomatology and GP consultations attenuated this effect.
Psychological symptoms				
Kuh, Wadsworth and Hardy, 1997[416]	See health symptoms section for details			
Hardy and Kuh, 2002[418]	Change in psychological symptoms (anxiety or depression, feelings of panic, tearfulness, irritability) and vasomotor symptoms reported between 1993 and 1998 (age 47-52) (inclusive)	Change in menopausal status in the previous 12 months	Life stress; prior psychological status and personality; health related behaviours; socioeconomic status; attitude to menopause	There was no significant change in psychological symptom reporting over the course of a year among women who changed from being pre-or peri-menopausal to being hysterectomised or among women who were already hysterectomised at the start of the year compared to women who remained pre-menopausal.
Kuh, Hardy, Rodgers and Wadsworth, 2002[419]	Psychological symptoms reported between ages 47 and 52 years	Family background, childhood characteristics, adult health, adult socioeconomic circumstances, social support and lifestyle, current life stress	Menopausal status (time-updated variable) (pre-menopausal, peri-menopausal, post-menopausal, hysterectomy, HRT user)	Hysterectomised women did not have significantly different psychological symptom scores compared to either pre-, peri- or post-menopausal women.

Quality of life				
Mishra and Kuh, 2006[420]	Perceived change in quality of life between age 47 and 54 years. Changes in 3 different quality of life domains were considered: physical health (physical health, energy level and body weight); psychosomatic status (nervous and emotional state, self-confidence, work life, ability to make decisions and ability to concentrate) and personal life (family life and time for self, hobbies, interests)	Change in menopausal status	Marital status, parity, occupational status at age 43 years, education, BMI at age 43 years, physical activity, current life stress	There was no significant change in any one of the three quality of life domains with transition from pre- or peri-menopause to hysterectomy or remaining hysterectomised compared to women who remained pre-menopausal
Sexual function				
Kuh, Wadsworth and Hardy, 1997[416]	See health symptoms section for details			
Mishra and Kuh, in press[421]	Self-reported change in sex life over the previous 12 months between ages 47 and 54 years	Change in menopausal status	BMI at age 43 years, marital status, parity, occupational class, educational qualifications, smoking, physical activity, other somatic symptoms (from previous factor analysis), psychological symptoms, current life stress	Women who underwent the transition from pre- or peri-menopausal to hysterectomy or who were hysterectomised at both time periods reported greater declines in sex life and greater levels of difficulty during intercourse compared to women who remained pre-menopausal. Women who underwent the transition to post-menopause reported similar declines and difficulties to hysterectomised women. .
Vasomotor symptoms				
Kuh, Wadsworth and Hardy, 1997[416]	See health symptoms section for details			
Hardy and Kuh, 2002[418]	Change in psychological and vasomotor symptoms (hot flushes, cold/night sweats) reported between 1993 and 1998 (age 47-52)(inclusive)	Change in menopausal status in the previous 12 months	Life stress; prior psychological status and personality; health related behaviours; socioeconomic status; attitude to menopause	There was no significant change in vasomotor symptom reporting over the course of a year with transition from pre- or peri-menopausal to hysterectomy or remaining hysterectomised compared to women who remained pre-menopausal.

Appendix 8: Unadjusted differences in mean values of measures of physical performance by characteristics of hysterectomy in the NSHD

Characteristic of hysterectomy	Regression coefficient (95% CI)			
	Chair rises ([1/time(seconds)] x 100)	Grip strength (kg)	Standing balance ($\log_e$ (time(seconds)))	Overall performance score
No hysterectomy or oophorectomy	0.00	0.00	0.00	0.00
Hysterectomy with oophorectomy	-0.06 (-0.33, 0.20)	-0.25 (-1.57, 1.06)	-0.08 (-0.21, 0.04)	-0.01 (-0.07, 0.06)
Hysterectomy no oophorectomy	-0.17 (-0.46, 0.11)	-0.76 (-2.16, 0.63)	-0.13 (-0.26, 0.003)	-0.07 (-0.14, -0.01)
Oophorectomy only	0.08 (-0.66, 0.82)	-1.46 (-4.96, 2.05)	-0.41 (-0.74, -0.08)	-0.10 (-0.26, 0.06)
p-value	*0.55*	*0.58*	*0.59*	*0.11*
No hysterectomy or oophorectomy	0.00	0.00	0.00	0.00
Hysterectomy for: Fibroids	0.04 (-0.28, 0.37)	0.04 (-1.54, 1.63)	-0.09 (-0.25, 0.06)	0.01 (-0.07, 0.08)
Menstrual disorders	0.07 (-0.27, 0.41)	-1.00 (-2.68, 0.68)	-0.06 (-0.22, 0.10)	-0.05 (-0.13, 0.03)
Prolapse	-0.56 (-1.17, 0.04)	-0.07 (-3.16, 3.02)	-0.16 (-0.45, 0.14)	-0.07 (-0.22, 0.07)
Cancer	-0.16 (-0.92, 0.59)	-0.49 (-4.29, 3.31)	-0.09 (-0.43, 0.25)	-0.04 (-0.21, 0.13)
Other reasons	-0.37 (-0.84, 0.10)	-0.80 (-3.14, 1.54)	-0.20 (-0.41, 0.02)	-0.07 (-0.18, 0.04)
Unknown reasons	-0.66 (-1.53, 0.20)	-0.88 (-5.07, 3.30)	-0.07 (-0.49, 0.36)	-0.12 (-0.33, 0.08)
p-value	*0.21*	*0.96*	*0.94*	*0.74*
No hysterectomy or oophorectomy	0.00	0.00	0.00	0.00
Route of hysterectomy: Abdominal	-0.14 (-0.36, 0.09)	-0.91 (-2.04, 0.22)	-0.08 (-0.19, 0.03)	-0.03 (-0.09, 0.02)
Vaginal	-0.11 (-0.55, 0.34)	0.81 (-1.36, 2.97)	-0.10 (-0.31, 0.10)	-0.04 (-0.14, 0.06)
Unknown	0.22 (-0.59, 1.03)	1.07 (-2.73, 4.86)	-0.44 (-0.81, -0.07)	-0.12 (-0.31, 0.06)
p-value	*0.70*	*0.25*	*0.18*	*0.65*
No hysterectomy or oophorectomy	0.00	0.00	0.00	0.00
Pre-menopausal hysterectomy	-0.10 (-0.31, 0.11)	-0.49 (-1.51, 0.53)	-0.09 (-0.19, 0.004)	-0.03 (-0.08, 0.01)
Post-menopausal hysterectomy	-0.62 (-1.72, 0.48)	-0.32 (-6.21, 5.57)	-0.47 (-0.99, 0.05)	-0.17 (-0.43, 0.09)
p-value	*0.36*	*0.95*	*0.16*	*0.31*

Note: p-values from likelihood ratio tests comparing models with categorisations of hysterectomy shown with a model in which all hysterectomies were grouped together (women with oophorectomy only excluded from all models except those examining oophorectomy status)

Appendix 9: Unadjusted associations between characteristics of hysterectomy and measures of functional limitation at age 53 years in the NSHD

Characteristic of hysterectomy	Total N	Difficulties walking 400 yards on level		Difficulties with stairs		Difficulties holding something heavy or removing a stiff lid	
		Yes N (%)	OR (95% CI)	Yes N (%)	OR (95% CI)	Yes N (%)	OR (95% CI)
No hysterectomy or oophorectomy	1148	130 (11.3)	1.00	197 (17.2)	1.00	235 (20.5)	1.00
Hysterectomy with oophorectomy	167	18 (10.8)	0.95 (0.56, 1.59)	38 (22.8)	1.42 (0.96, 2.11)	54 (32.3)	1.86 (1.30, 2.65)
Hysterectomy no oophorectomy	150	23 (15.3)	1.42 (0.88, 2.29)	31 (20.7)	1.26 (0.82, 1.92)	37 (24.7)	1.27 (0.85, 1.89)
Oophorectomy only	20	3 (15.0)	1.38 (0.40, 4.78)	8 (40.0)	3.22 (1.30, 7.98)	6 (30.0)	1.67 (0.63, 4.38)
p-value			*0.23*		*0.65*		*0.13*
No hysterectomy or oophorectomy	1148	130 (11.3)	1.00	197 (17.2)	1.00	235 (20.5)	1.00
Hysterectomy for: Fibroids	106	10 (9.4)	0.82 (0.41, 1.60)	24 (22.6)	1.41 (0.87, 2.28)	33 (31.1)	1.76 (1.14, 2.71)
Menstrual disorders	100	16 (16.0)	1.49 (0.85, 2.62)	20 (20.0)	1.21 (0.72, 2.02)	30 (30.0)	1.67 (1.06, 2.61)
Prolapse	28	5 (17.9)	1.70 (0.64, 4.55)	6 (21.4)	1.32 (0.53, 3.29)	6 (21.4)	1.06 (0.42, 2.64)
Cancer	19	1 (5.3)	0.44 (0.06, 3.29)	4 (21.1)	1.29 (0.42, 3.92)	5 (26.3)	1.39 (0.49, 3.89)
Other reasons	48	5 (10.4)	0.91 (0.35, 2.34)	11 (22.9)	1.44 (0.72, 2.86)	12 (25.0)	1.30 (0.66, 2.53)
Unknown reasons	16	4 (25.0)	2.61 (0.83, 8.21)	4 (25.0)	1.61 (0.51, 5.04)	5 (31.3)	1.77 (0.61, 5.13)
p-value			*0.33*		*0.996*		*0.90*
No hysterectomy or oophorectomy	1148	130 (11.3)	1.00	197 (17.2)	1.00	235 (20.5)	1.00
Route of hysterectomy: Abdominal	241	26 (10.8)	0.95 (0.61, 1.48)	51 (21.2)	1.30 (0.92, 1.83)	71 (29.5)	1.62 (1.19, 2.22)
Vaginal	57	11 (19.3)	1.87 (0.95, 3.71)	12 (21.1)	1.29 (0.67, 2.48)	13 (22.8)	1.15 (0.61, 2.17)
Unknown	19	4 (21.1)	2.09 (0.68, 6.39)	6 (31.6)	2.23 (0.84, 5.93)	7 (36.8)	2.27 (0.88, 5.82)
p-value			*0.15*		*0.59*		*0.43*
No hysterectomy or oophorectomy	1148	130 (11.3)	1.00	197 (17.2)	1.00	235 (20.5)	1.00
Pre-menopausal hysterectomy	309	40 (12.9)	1.16 (0.80, 1.70)	68 (22.0)	1.36 (1.00, 1.86)	88 (28.5)	1.55 (1.16, 2.06)
Post-menopausal hysterectomy	8	1 (12.5)	1.12 (0.14, 9.16)	1 (12.5)	0.69 (0.08, 5.64)	3 (37.5)	2.33 (0.55, 9.82)
p-value			*0.97*		*0.49*		*0.59*

Note: p-values from likelihood ratio tests comparing models with categorisations of hysterectomy shown with a model in which all hysterectomies were grouped together (women with oophorectomy only excluded)

Appendix 10: The 28 items of the General Health Questionnaire

GHQ01 "perfectly well and in good health"

GHQ02 "in need of a good tonic"

GHQ03 "run down and out of sorts"

GHQ04 "felt that you are ill"

GHQ05 "getting any pains in your head"

GHQ06 "been getting a feeling of tightness or pressure in your head"

GHQ07 "having hot or cold spells"

GHQ08 "lost much sleep over worry"

GHQ09 "had difficulty in staying asleep once you are off"

GHQ10 "been managing to keep yourself busy and occupied"

GHQ11 "been taking longer over the things you do"

GHQ12 "felt on the whole you were doing things well"

GHQ13 "been satisfied with the way you've carried out your task"

GHQ14 "felt that you are playing a useful part in things"

GHQ15 "felt capable of making decisions about things"

GHQ16 "felt constantly under strain"

GHQ17 "been able to enjoy your normal day to day activities"

GHQ18 "been getting edgy and bad tempered"

GHQ19 "been getting scared or panicky for no good reason"

GHQ20 "found everything getting on top of you"

GHQ21 "been thinking of yourself as a worthless person"

GHQ22 "felt that life is entirely hopeless"

GHQ23 "been feeling nervous and strung up all the time"

GHQ24 "felt that life isn't worth living"

GHQ25 "thought of the possibility that you might make away with yourself"

GHQ26 "found at times you couldn't do anything because your nerves were too bad"

GHQ27 "found yourself wishing you were dead and away from it all"

GHQ28 "found the idea of taking your own life kept coming into your mind"

Appendix 11: Unadjusted associations between characteristics of hysterectomy and self-perceived effect of hysterectomy on quality of life and wellbeing (Total N=316)

		Effect of hysterectomy on quality of life and wellbeing N(row %)			p-value*	Relative risk (95% CI) of:	
		Very good or good	Neither good nor bad	Bad or very bad		perceiving neither a good nor a bad effect	perceiving a bad or very bad effect
Route of operation	Abdominal	208 (82.2)	33 (13.0)	12 (4.7)	0.60	1.00	1.00
	Vaginal	55 (90.2)	4 (6.6)	2 (3.3)		0.46 (0.16, 1.35)	0.63 (0.14, 2.90)
	Keyhole/unknown	2 (100)	0 (0)	0 (0)		-	-
Age at time of operation (years)	< 40	74 (85.1)	9 (10.3)	4 (4.6)	0.35	1.00	1.00
	40 – 44	65 (89.0)	5 (6.9)	3 (4.1)		0.63 (0.20, 1.98)	0.85 (0.18, 3.96)
	45 – 49	73 (83.9)	9 (10.3)	5 (5.8)		1.01 (0.38, 2.70)	1.27 (0.33, 4.91)
	≥50	51 (77.3)	13 (19.7)	2 (3.0)		2.10 (0.83, 5.27)	0.73 (0.13, 4.11)
Menopausal status at time of operation							
	Pre/peri-menopausal	256 (84.5)	34 (11.2)	13 (4.3)	0.34	1.00	1.00
	Post-menopausal	9 (69.2)	3 (23.1)	1 (7.7)		2.51 (0.65, 9.73)	2.19 (0.26, 18.59)

* p-value from chi-squared test

Appendix 12: Unadjusted associations between indicators of health status at age 53 years and self-perceived effect of hysterectomy on quality of life and wellbeing (Total N=316)

		Effect of hysterectomy on quality of life and wellbeing N(row %)			p-value*	Relative risk (95% CI) of:	
		Very good or good	Neither good nor bad	Bad or very bad		perceiving neither a good nor a bad effect	perceiving a bad or very bad effect
Difficulty climbing stairs	No	192 (84.6)	27 (11.9)	8 (3.5)	0.28	1.00	1.00
	Yes	48 (78.7)	8 (13.1)	5 (8.2)		1.19 (0.51, 2.77)	2.5 (0.78, 7.98)
Difficulty walking	No	212 (83.5)	32 (12.6)	10 (3.9)	0.38	1.00	1.00
	Yes	28 (82.4)	3 (8.8)	3 (8.8)		0.71 (0.20, 2.47)	2.27 (0.59, 8.75)
Difficulty gripping	No	175 (83.7)	25 (12.0)	9 (4.3)	0.95	1.00	1.00
	Yes	65 (82.3)	10 (12.7)	4 (5.1)		1.08 (0.49, 2.37)	1.20 (0.36, 4.02)
Chair rise time	1 (Best)	81 (81.8)	11 (11.1)	7 (7.1)	0.30	1.00	1.00
	2	77 (83.7)	14 (15.2)	1 (1.1)		1.34 (0.57, 3.13)	0.15 (0.02, 1.25)
	3	69 (83.1)	9 (10.8)	5 (6.0)		0.96 (0.38, 2.45)	0.84 (0.25, 2.76)
Grip strength	1 (Best)	79 (85.9)	11 (12.0)	2 (2.2)	0.09	1.00	1.00
	2	81 (79.8)	15 (16.9)	3 (3.4)		1.52 (0.65, 3.52)	1.67 (0.27, 10.28)
	3	80 (84.2)	7 (7.4)	8 (8.4)		0.63 (0.23, 1.70)	3.95 (0.81, 19.18)
Standing balance	1 (Best)	74 (84.1)	9 (10.2)	5 (5.7)	0.92	1.00	1.00
	2	98 (81.7)	17 (14.2)	5 (4.2)		1.43 (0.60, 3.38)	0.76 (0.21, 2.70)
	3	55 (82.1)	9 (13.4)	3 (4.5)		1.35 (0.50, 3.61)	0.81 (0.19, 3.52)
BMI (kg/m^2)	≤ 25	69 (78.4)	15 (17.1)	4 (4.6)	0.49	1.00	1.00
	25.1 – 30	100 (85.5)	11 (9.4)	6 (5.1)		0.51 (0.22, 1.17)	1.04 (0.28, 3.80)
	> 30	69 (86.3)	8 (10.0)	3 (3.8)		0.53 (0.21, 1.34)	0.75 (0.16, 3.48)

Note: For tertiles of physical performance 1=Best performance 2=Intermediate 3=Poor performance

* p-value from chi-squared test

Appendix 13: Unadjusted associations between indicators of lifetime socioeconomic position, cognition, parity and self-perceived effect of hysterectomy on quality of life and wellbeing (Total N=316)

		Effect of hysterectomy on quality of life and wellbeing N(row %)			p-value*	Relative risk (95% CI) of:	
		Very good or good	Neither good nor bad	Bad or very bad		perceiving neither a good nor a bad effect	perceiving a bad or very bad effect
Father's occupational class	I or II	50 (84.8)	5 (8.5)	4 (6.8)	0.88	1.00	1.00
	IIINM	47 (83.9)	7 (12.5)	2 (3.6)		1.49 (0.44, 5.02)	0.53 (0.09, 3.04)
	IIIM	80 (85.1)	11 (11.7)	3 (3.2)		1.38 (0.45, 4.19)	0.47 (0.10, 2.18)
	IV or V	66 (80.5)	12 (14.6)	4 (4.9)		1.82 (0.60, 5.50)	0.76 (0.18, 3.18)
Maternal education	1 (High)	16 (72.7)	4 (18.2)	2 (9.1)	0.60	1.00	1.00
	2	26 (83.9)	3 (9.7)	2 (6.5)		0.46 (0.09, 2.34)	0.62 (0.08, 4.81)
	3	32 (80.0)	7 (17.5)	1 (2.5)		0.88 (0.22, 3.43)	0.25 (0.02, 2.97)
	4 (Low)	151 (85.8)	18 (10.2)	7 (4.0)		0.48 (0.14, 1.58)	0.37 (0.07, 1.94)
Educational level							
	Advanced secondary or higher	65 (85.5)	9 (11.8)	2 (3.0)	0.23	1.00	1.00
	Ordinary secondary	72 (88.9)	6 (7.4)	3 (3.7)		0.60 (0.20, 1.78)	1.35 (0.22, 8.36)
	Below secondary	26 (76.5)	4 (11.8)	4 (11.8)		1.11 (0.31, 3.93)	5.00 (0.86, 28.98)
	None	83 (79.1)	17 (16.2)	5 (4.8)		1.48 (0.62, 3.53)	1.96 (0.37, 10.42)
Own occupational class	I & II	89 (84.8)	10 (9.5)	6 (5.7)	0.41	1.00	1.00
	IIINM	86 (85.2)	14 (13.9)	1 (1.0)		1.45 (0.61, 3.44)	0.17 (0.02, 1.46)
	IIIM	17 (73.9)	4 (17.4)	2 (8.7)		2.09 (0.59, 7.46)	1.75 (0.32, 9.38)
	IV & V	56 (82.4)	8 (11.8)	4 (5.9)		1.27 (0.47, 3.41)	1.06 (0.29, 3.92)
Cognition at age 8 years	1 (High)	51 (85.0)	8 (13.3)	1 (1.7)	0.53	1.00	1.00
	2	65 (89.0)	5 (6.9)	3 (4.1)		0.49 (0.15, 1.59)	2.35 (0.24, 23.31)
	3	66 (82.5)	11 (13.8)	3 (3.8)		1.06 (0.40, 2.83)	2.32 (0.23, 22.95)
	4 (Low)	53 (79.1)	9 (13.4)	5 (7.5)		1.08 (0.39, 3.02)	4.81 (0.54, 42.61)
Parity	0	16 (80.0)	3 (15.0)	1 (5.0)	0.68	1.00	1.00
	1	30 (85.7)	4 (11.4)	1 (2.9)		0.71 (0.14, 3.57)	0.53 (0.03 (9.11)
	2	119 (88.2)	12 (8.9)	4 (3.0)		0.54 (0.14, 2.11)	0.54 (0.06, 5.12)
	3	58 (78.4)	12 (16.2)	4 (5.4)		1.10 (0.28, 4.39)	1.10 (0.12, 10.58)
	≥4	29 (76.3)	6 (15.8)	3 (7.9)		1.10 (0.24, 5.02)	1.66 (0.16, 17.25)

* p-value from chi-squared test

Maternal education: 1 = Secondary and further or higher education ; 2 = Secondary only or Primary and further or higher education ; 3 = Primary and further education (no qualifications) ; 4 = Primary education only